St. Lideta Health Science& Business College

Department of Pharmacy

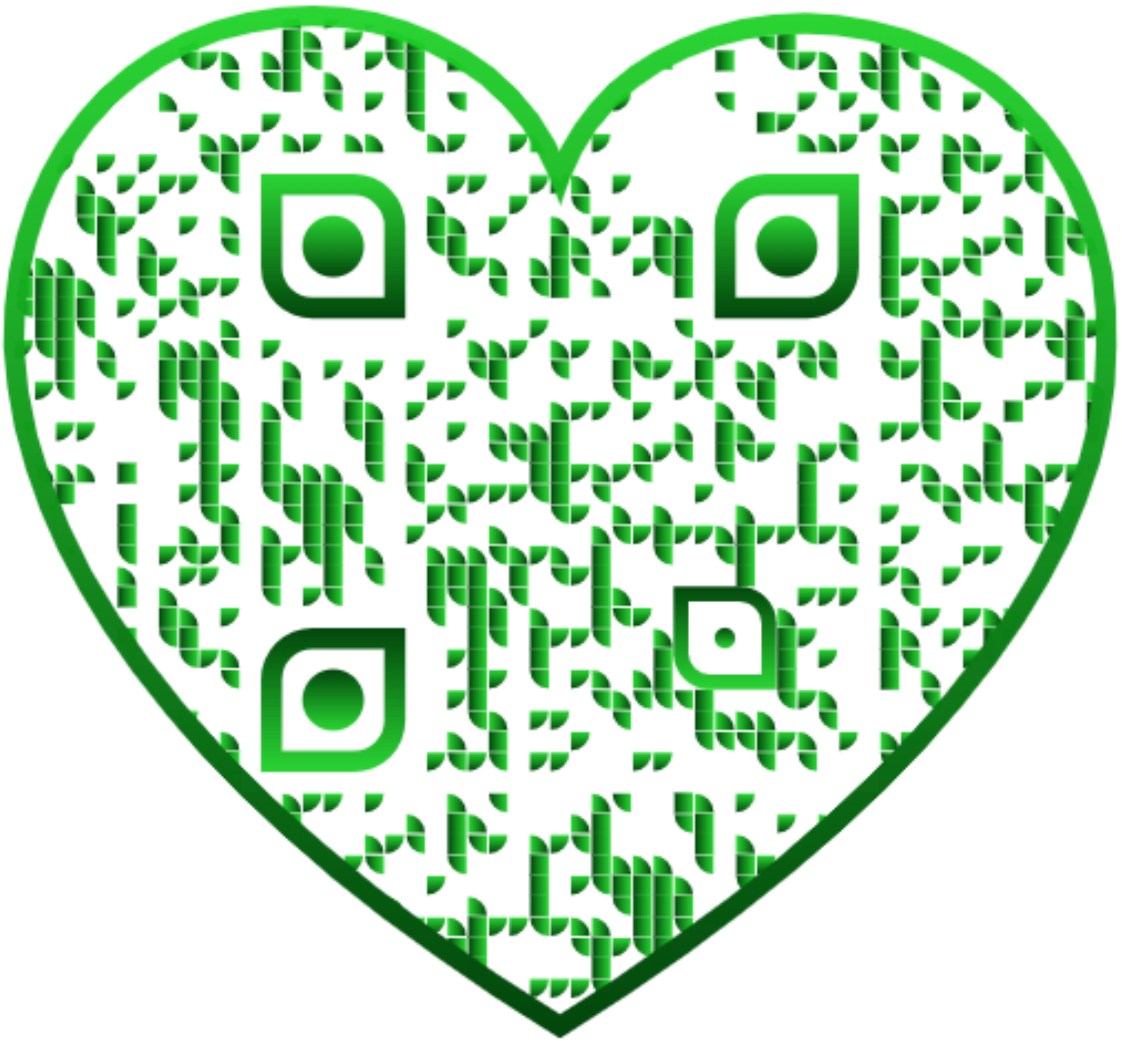
COURSE TITLE: Industrial pharmacy: 4 cr. hrs

Lecture note for pharmacy degree students

INSTRUCTOR: Tesfu Negussie

QUALIFICATION

- **MPH**
- **MSC**
- **BA**
- **Bpharm**



Course synopsis

1. Fundamentals

- Flow of Fluids
- Heat transfer
- Mass transfer

2. Unit operations

- Leaching & extraction
- Evaporation & Concentration
- Filtration
- Reverse Osmosis
- Centrifugation
- Distillation
- Crystallization
- Size reduction
- Size separation
- Mixing
- Drying

3. Particle size and powder technology
4. Granulation
5. Tablets and compaction
6. Tablet Coating
7. Capsules
8. Pharmaceutical Aerosols
9. Modified release dosage forms
10. Sterile products
11. Current good manufacturing practices [cGMP]

Teaching Methodology

- ❖Lecture
- ❖Discussion

Assessment methods

- ❖Formative assessment[Test , quiz, mid exam]... 50%
- ❖Final exam……..... 50%

References

1. Tutorial pharmacy: Cooper & Gunn's
2. Ansels Pharmaceutical Dosage Forms and Drug Delivery Systems 8th edition , 2004
3. Modern Pharmaceutics by Gilbert S. Banker , 4th edition, 2002, Marcel Dekker
4. The Theory and Practice of Industrial Pharmacy by Leon Lachman, Herbert A. Lieberman, Joseph L. Kanig. 3rd edition, 1986, Lea & Febiger
5. Physical Pharmacy: Physical Chemical Principles in Pharmaceutical Sciences by Alfred Martin, 4th edition, 1993
6. Handbook of Pharmaceutical Excipients by Arthur H. Kibbe ,3rd edition Vol 3, 2000, Amer. Pharmaceutical Assoc

Introduction:

Pharmaceutical manufacturing processes can be divided into a number of unit operations based on a few fundamental principles

Fundamentals

- Basic operations that serve as a starting point for any pharmaceutical processes
- Involved in all unit operations
- Controlled in all unit operations
- Include:
  - Flow of Fluids
  - Heat transfer
  - Mass transfer

Flow of Fluids /Fluid dynamics

- Fluids refer to liquid, Vapour /gas
- All unit operations involve movement of a fluid through pipes or channels or between or around particles

Fluid dynamics

- Study of the behavior of fluids
- In chemical processes fluid streams flow from one process to another through pipes and ducts/hose.
- Process fluids are moved by pumps and compressors
- Fluid flow rates must be monitored by meters and are controlled by valves

Mechanism of fluid flow

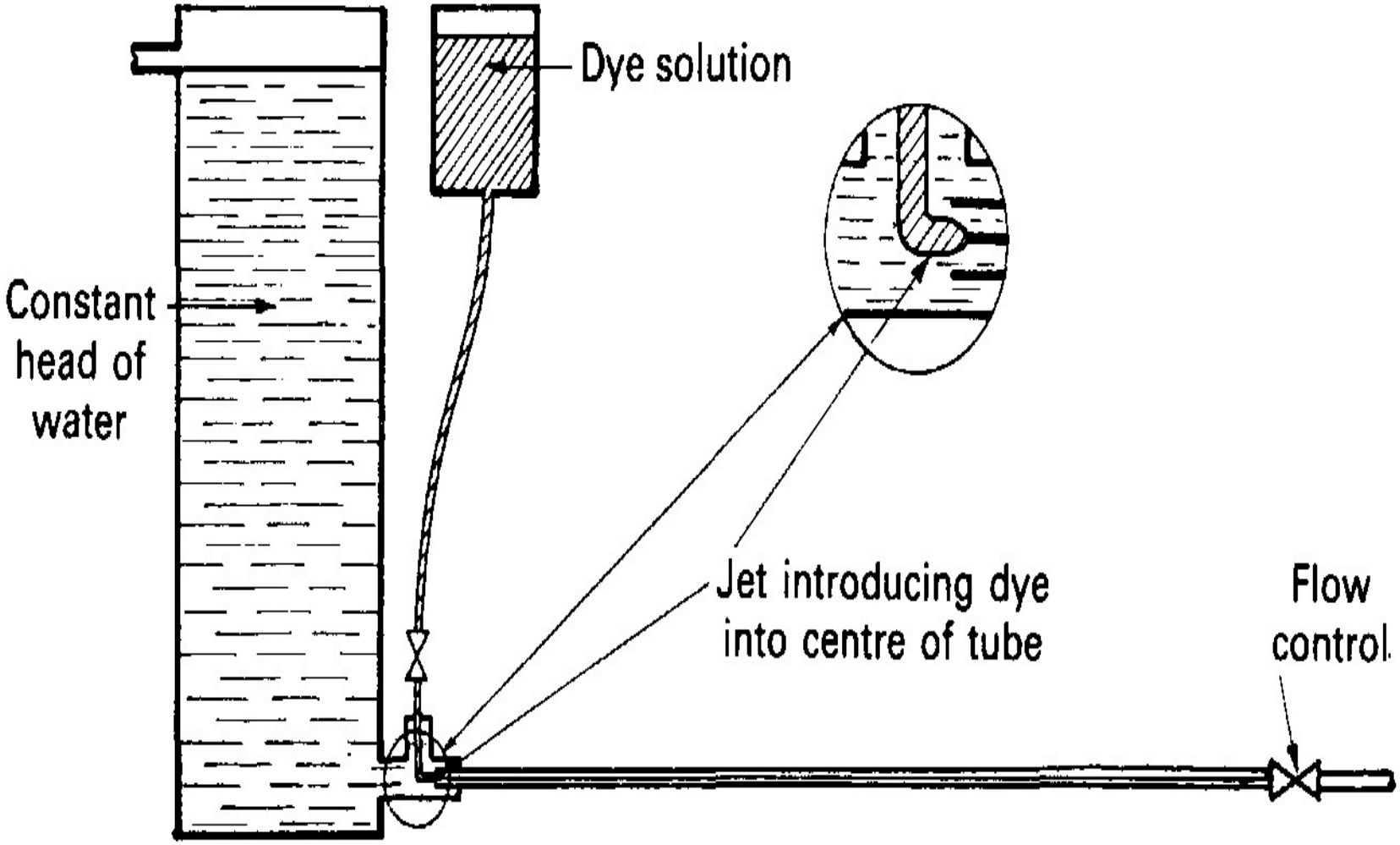
Character of fluid flow via pipe or channel varies depending on conditions of flow:

- Density of fluid [ρ]
- Viscosity of fluid [η]
- Velocity [V]
- Diameter of pipe[d]
- Surface texture of the pipe[rough or smooth]

Osborne Reynolds[1883] conducted experiment by changing conditions of flow

Reynolds experiment

- Long glass tube was connected to reservoir
- Reservoir provides a constant head of water
- Reservoir has control valve at out let
- Flow control valve enables to vary rate of flow
- Reynolds varied flow velocity
- Then ,observed fluid flow pattern



Reynolds' apparatus

Reynolds made the following observations:

1. At low velocity

- ❖ Thread of coloured liquid remains undisturbed in the centre of water stream
- ❖ Water moves steadily along the tube hence no mixing occurs
- ❖ Streamlines, viscous or laminar flow occurs

2. At moderate velocity[Critical velocity]

- ❖ Threads of coloured liquids begins to waver
- ❖ No mixing occurs but Transitional flow occurs

3. At high velocity

- ❖ Eddies[spiral or circular movement] begin to occur in the flow
- ❖ Coloured liquid mixes with bulk of water, immediately after leaving the jet, resulting in turbulent flow.

- Reynolds' experiments indicated that flow conditions were affected by four factors, namely the diameter of the pipe & viscosity, density and velocity of the fluid
- Reynolds established intricate link among the four flow conditions :

$$\mathbf{Re} = \frac{\rho * \mathbf{u} * \mathbf{d}}{\eta}$$

Where,
P= density of fluid
η= viscosity of fluid
U = flow speed of fluid
Re = Reynolds number which is dimensionless, i.e., $Re = \frac{Kg}{m^3} * \frac{m}{S} * m * \frac{1}{\frac{Kg}{m.S}} = \frac{Kg}{m^3} * \frac{m}{S} * m * \frac{m*S}{Kg}$

Significance of Reynolds Number, Re

Enables to predict character of flow in a particular set of conditions based on the value of Re. **How?**

- If Re <2000, the flow is streamline
- If Re >4000, the flow is turbulent
- If 2000<Re< 4000 , the flow type can be streamline or turbulent depending on inner texture of the tube
  - Rough texture results in turbulent flow
  - Smooth texture results in laminar flow

When do you think mixing occurs ? Why?

Note:

- In streamline flow, the average velocity is 0.5 of the maximum
- In turbulent flow, the average velocity is 0.8 of the maximum

Reason: There is movement at right angles to the direction of flow in the later flow type

Heat Transfer

Heat Transfer

Introduction

- Major unit operation in pharmacy
- Process fluids may need to be heated up to a certain temperature, creating temperature gradient
- Occurs only from a region of higher temperature to a region of lower temperature

Mechanisms of heat transfer

- Conduction
- Convection
- Radiation

Note:

It is unusual for heat transfer to take place by one mechanism only

Conduction

- The most widely understood mechanism of heat transfer
- The main method of heat transfer in solids
- Flow of heat depends upon the transfer of vibration energy from one molecule to another and, in the case of metals, the movement of free electrons
- No mixing action is involved
- When heat is flowing under steady-state conditions, the quantity of heat transferred[q] is given by:

$$Q = \frac{KA\Delta T\theta}{L} \qquad q = \frac{KA\Delta T}{L}$$

where,

ΔT = change in temperature

q = quantity of heat transferred per unit time

Q = quantity of heat transferred

K = coefficient of thermal conductivity

L= Thickness

A = area

θ = Time

Example

Calculate amount of heat transferred via a sheet of metal 10 mm in thickness,0.6 m wide & 1 m long in 30 minutes with a temperature of 70 & 30 ^{o}K on opposite sides and coefficient of thermal conductivity is 43W/m ^{o}K

Solution

$Q = KA(\Delta T)\Theta/L$

$= 43 \times [(0.6m \times 1m)(70-30)(30\ min \times 60\ sec/min)]/0.01m$

$= 185.76 \times 10^{6}$ Joules

Convection

- Heat is transferred from or to a region by motion of fluids
- Heat transfer to a fluid begins by conduction via the boundary layer
- In the bulk of the fluid, the rise in temperature triggers change in density & viscosity, setting up convection currents
- In natural convection, the movement is caused by buoyancy forces induced by variations in the density of the fluid caused by differences in temperature
- In forced convection, movement is created by an external agency such as a pump or stirrer

Radiation

- All bodies with a temperature above absolute zero radiate heat in the form of electromagnetic waves
- Radiation may be transmitted, reflected, or absorbed by matter, the fraction absorbed being transformed into heat
- Radiation is of great importance at very high or very low temperatures and under circumstances in which the other modes of heat transmission are suppressed
- Radiation is rare in solids but examples are found among glasses and plastics
- Least important from the view of pharmaceutical processing

Mass transfer

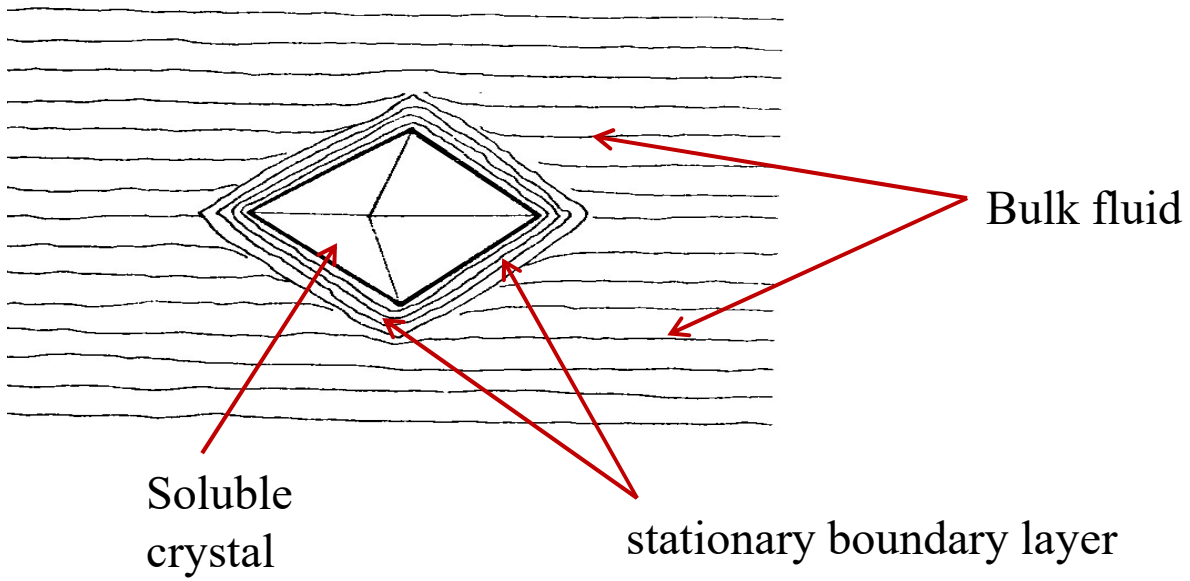
Introduction

Involves transfer of mass

- from a solid to a fluid, a condition called as solid/fluid mass transfer
- between two immiscible fluids (two liquids, or one liquid & a gas (or vapor) which is called as fluid to fluid mass transfer

Solid/fluid mass transfer

Consider a soluble crystal immersed into a solvent such that the crystal is surrounded by a stationary boundary layer of the solute within the bulk of the moving fluid. If the movement of the bulk is due to change in temperature accompanied by change in its density or viscosity, then such movement is called natural convection. But if movement of the bulk is due to agitation or pump, such movement is called forced convection



Solid/fluid mass transfer involves molecular & Eddy diffusions

Molecular diffusion

Refers to movement of molecules via boundary layer without mechanical mixing or movement. It is analogues to heat transfer by conduction

Eddy diffusion

Occurs after materials have passed via boundary layer. It involves mass transfer due to bulk movement of the solution

- ✓Analogues to heat transfer by convection

$$W = \frac{DA(C_1 - C_2)\theta}{L} \quad or \quad w = \frac{DA(C_1 - C_2)}{L}$$

Where;

C1 = concentration of solute at interface
C2 = concentration of solute in the bulk

w = Weight of solute diffusing in unit time

W= Weight of solute diffusing
D = Diffusion coefficient weight of solute

L= Film thickness

A = area

θ = Time

Note: The rate of molecular diffusion via the boundary layer limits the rate of solubility of the crystal

Fluid/ Fluid mass transfer[Liquid-liquid extraction]

Occurs between two immiscible fluids (two liquids or a liquid & a gas (or vapor)

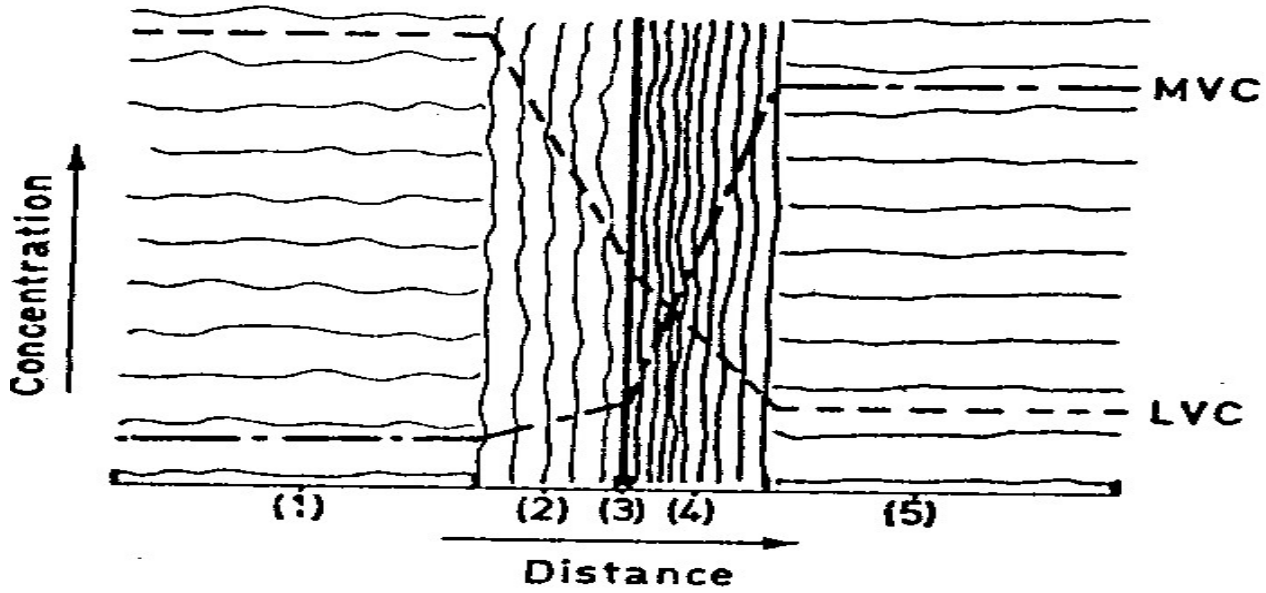


Fig. 13.3 Concentration gradients in fluid/fluid system

(1) vapour (2) vapour film (3) interface (4) liquid film (5) liquid

MVC = more volatile component
LVC = less volatile component

Note

1. Size reduction, Agitation & /or elevated temperature facilitate rate of mass transfer. ……How?

Size reduction of the solid

Increase the area over which diffusion during dissolution or solvent penetration , during extraction or heat based vapor removal during drying can occur

Agitation: Decreases thickness of boundary layers & disperse any local concentration of solution & thereby increasing concentration gradient

Elevated temperature: Increases solubility & diffusion coefficient of most substances, decreases viscosity of the liquid, so reducing thickness of the boundary layer

2.Mass transfer is involved in any pharmaceutical unit operation that engages phase change. Thus, design of mass transfer equipment must consider heat transfer & turbulent flow conditions, maximum conc., &/or partial pressure gradients and largest possible surface area.

2. Unit operations

- Leaching & extraction
- Evaporation
- Concentration
- Drying
- Size reduction & separation
- Mixing
- Filtration
- Centrifugation
- Crystallization

Leaching & extraction

Extraction

- Removal of soluble material from an insoluble residue, either liquid or solid , by treatment with liquid solvent
- Thus, extraction is a solution process that depends on mass transfer phenomena
- Rate of extraction is controlled by rate of diffusion of solute via liquid boundary layer or layers at interface
- Solvent extraction process is entailed in preparation of most drugs either from plant , animal or synthetic origin.
- Although, with the advent of synthetic drugs, demand for drugs from natural source is diminishing, alkaloids, glycosides, fixed & volatile oils, proteins & polypeptides are still extracted from plant & animal origin

Separation of active constituent is desirable

Why?

Reasons

- Potency is readily controlled
- Drug spoilage by enzyme action can be alleviated
- Preparation of drug is easily formulated ,more stable, elegant & palatable if made from pure active agent
- Injection of crude drug is dangerous
- Small bulk facilitate storage & transportation

Leaching: Removal of a soluble constituent from solid by means of a solvent via maceration &/or percolation

What is the difference b/n extraction & leaching ?

1. Extraction is wider in scope & most widely used in pharmaceutics than leaching
2. Extraction involves both liquid/liquid & solid/liquid while leaching entailed removal of soluble constituents only from the later type
3. Leaching yields crude extracts that can be used as inputs for liquid/liquid extraction so as to fractionate into their separate pure state

- **Solid/liquid extraction** can be done from plant[roots ,leaves, barks, stems , fruits, seeds, etc] and animal tissues, & organs or fermentation medium for synthetic drugs by maceration or percolation
- **Liquid/liquid extraction** leads to purification of extracts acquired by leaching using solvents that is immiscible with primary solvent in the separation funnel

Reason

- Leaching yields products containing several extractable constituents in the extraction solvents
- Such constituents should be individually isolated in their relatively pure state using appropriate immiscible solvents

Sequential activities involved in drug extraction process include:

- Comminution
- Solvent penetration into extractable material
- Dissolution of soluble cellular content
- Escape of dissolved constituents via cell walls & solvent boundary layers surrounding the drug
- Separation of soluble extract from the marc

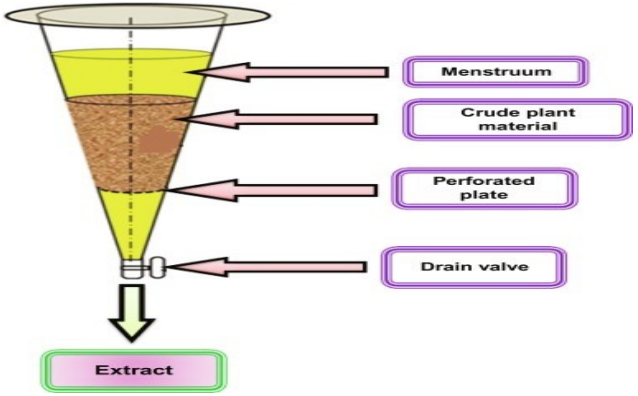
General characteristics of solvents used for drug extraction

- Cheap
- Non-toxic
- Stable[chemically & physically inert]
  - have neutral reaction
  - Not too volatile
  - Non-inflammable
- Selective: Removes desired constituents only

Extraction methods

Small scale extraction methods

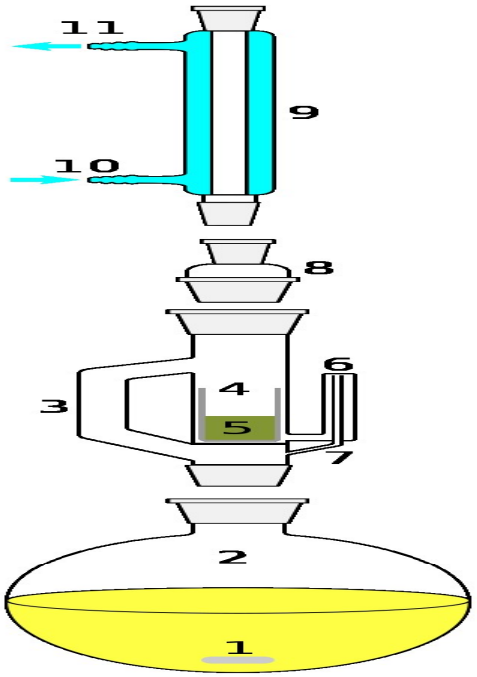
- Maceration
- Percolation
- Reserve percolation
- Soxhlet extraction [Continuous extraction]

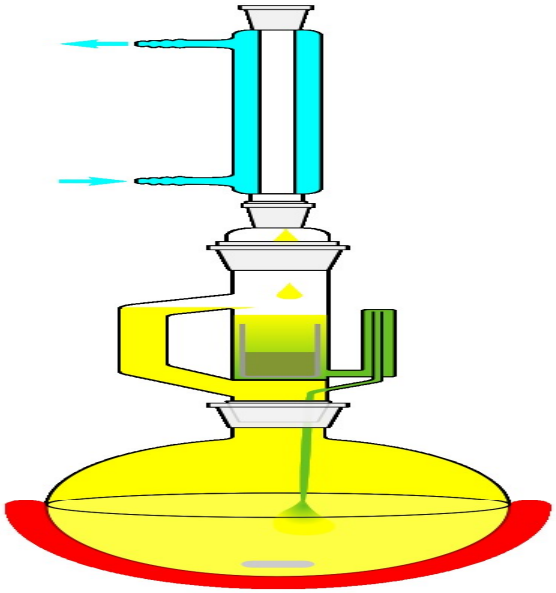


Large scale extraction methods

- Circulatory extraction
- Multiple stage extraction
- Continuous extraction

Schematic representation of a Soxhlet extractor





Parts of a Soxhlet extractor

1: Stirrer bar
2: Still pot
3. Distillation path
4: Thimble

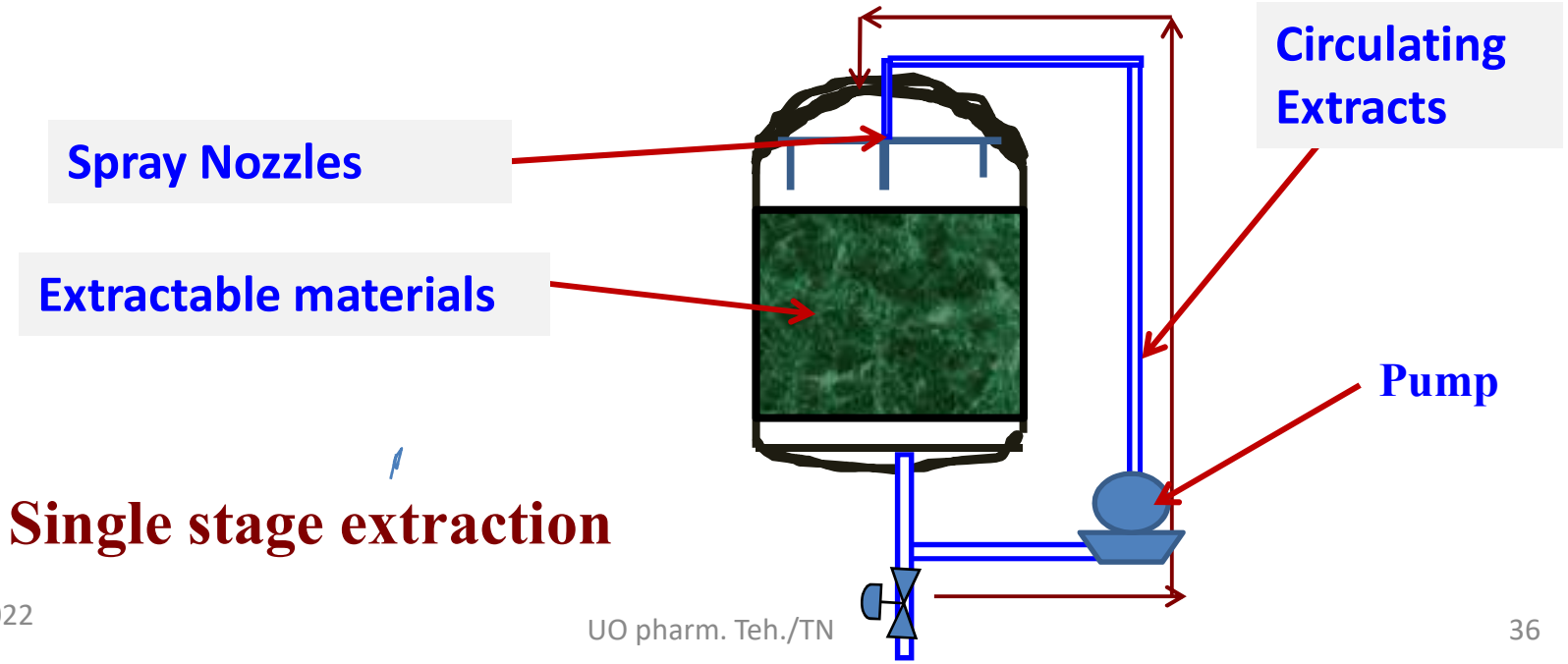
5. Drug
6: Siphon top
7. Siphon exit

8. Expansion adapter
9: Condenser
10: Cooling water in
11: Cooling water out

Note: The still pot should not be overfilled and the volume of solvent in the still pot should be 3 to 4 times the volume of the Soxhlet chamber

Circulatory extraction

- Type of maceration process where by solvent is continuously circulating
- Solvent is pumped from bottom of extraction vessel to inlet to re-spray over medicinal material via spray nozzles
- Thus, extraction is improved as compared to simple maceration extraction



Single stage extraction

Advantages of solvent movement

- Reduce thickness of boundary layer
- Minimizes local solvent concentration and facilitates uniform solvent distribution
- Efficient extraction within short time

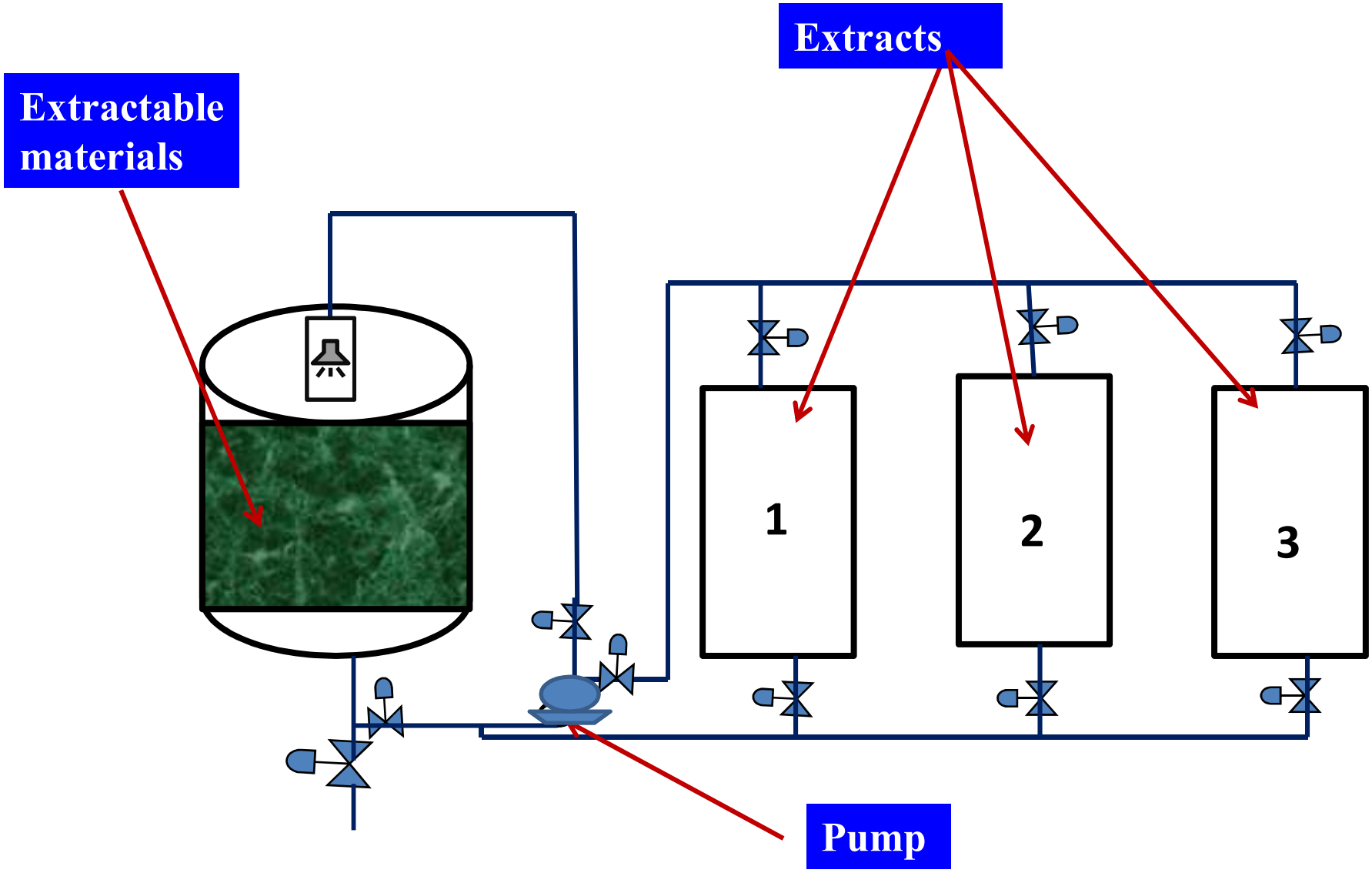
Disadvantage of single stage circulatory extraction process

Extraction is incomplete like simple maceration

Reason

Mass transfer will cease as soon as equilibrium is set up

Multiple stage extraction



Procedure

1. Fill extractor with drug, add solvent and circulate. Run off to receiver 1.
2. Refill extractor with solvent and circulate. Run off to receiver 2.
3. Refill extractor with solvent and circulate. Run off to receiver 3.
4. Remove mark from extractor and recharge.
5. Return solution from 1 to extractor. Remove for evaporation.
6. Return solution from 2 to extractor and circulate. Run off to receiver 1.
7. Return solution from 3 to extractor and circulate. Run off to receiver 2.
8. Add fresh solvent to extractor and circulate. Run off to receiver 3.
9. Remove mark from extractor and recharge. Repeat cycle.

Advantages

- The drug is extracted as many times as there are receivers – in this case, three
- If more extraction stages are required, it is only necessary to have more receivers
- The last treatment of the mark before it is discharged is with fresh solvent, giving maximum extraction.
- The solution is in contact with fresh drug before removal for evaporation, giving the highest possible concentration

Factors affecting choice of extraction process

- Drug character
  - If Hard & though , use percolation
  - If soft & parenchymatous or unpwoderable use maceration
- Therapeutic value of the drug
  - Invaluable therapeutic value needs maximum extraction while for little ones maceration suffices
- Drug stability
  - Avoid continuous extraction for thermo-labile drug
- Cost of the drug
  - Complete extraction is needed using percolation for expensive drug & simple maceration for cheap drug

Evaporation [Concentration]

- Vaporization of a portion of a solvent from solution of a solid in order to obtain concentrated liquid residue. It is free escape of a vapor from surface of liquid below its boiling points.
- In industrial practice however, evaporation is carried out at boiling point of a liquid using latent heat of vaporization in order to secure rapid removal of vapor
- The vapor is not condensed but withdrawn & concentrated liquid residue is collected
- Used to isolate non-volatile concentrated solute residue from solution
- In general, rate of vaporization is controlled by rate of heat transfer
- Evaporators are designed, therefore, to give maximum heat transfer, largest possible area, suitable temperature gradient & reduced boundary layers

Factors affecting Evaporation

1. Temperature : Optimal temperature level & suitable evaporator must be selected by considering heat-sensitivity level of product to be collected as concentrated residue. For instance alkaloids, glycosides, enzymes, hormones and some antibiotics are extremely thermolabile, hence demand special dryers
2. Temperature & time of evaporation: Exposure to a relatively high temperature for a short period of time may be less destructive of active principles than a lower temperature with exposure for a longer period
3. Temperature & moisture content: Some drugs get easily hydrolysed in the presence of moisture at elevated temperature

4. Type of product required: Determines type of method & apparatus to be used.

   For example, evaporating pans or stills produce liquid or dry products while film evaporators yield only liquid products

5. Liquor concentration:

   As the liquor becomes concentrated, viscosity & boiling point of the solution are elevated, thicker boundary layers are formed, solid deposit build up on heating surface.

   The ultimate outcomes are greater risk of damage to thermolabile constituents and temperature gradient reduction by reducing heat transfer (rate of heat transfer).

   Therefore, to minimize these problems, evaporator equipped with turbulent flow conditions should be employed.

6. Stability of drug: Avoid continuous extraction of extractable materials having thermo-labile drug constituents

Types of pharmaceutical Evaporators

Steam operating pharmaceutical evaporators are categorized into three based on forms of movement involved to facilitate heat transfer

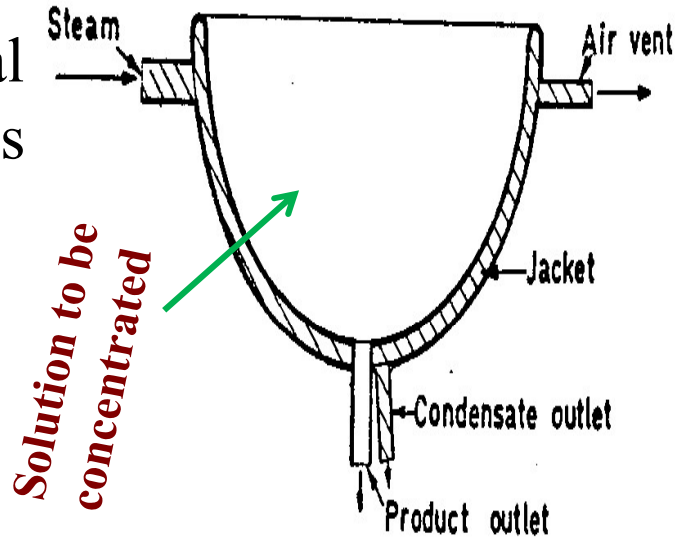
1. Natural circulation evaporators
2. Forced circulation evaporators
3. Film evaporators

1. Natural circulation evaporators

The movement of the liquid results from convection current set up by the heating process resulting in boiling of the liquor

A. Evaporating pans

It is hemispherical simplest form of natural circulation evaporator , made of stainless steel & surrounded by a steam jacket



Evaporating pan

Advantages

- Simple & cheap to construct
- Easy to use, clean & maintain

Disadvantages

Overall coefficient of heat transfer is poor as it depends only on natural convection & solids can be deposited on heating surfaces there by increasing thickness of boundary layer

B. Evaporating stills [Stills]:

It is a modified form of evaporating pans

Advantages

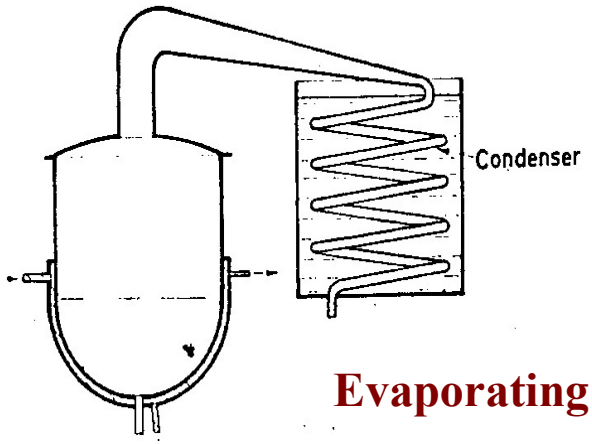
- Simple to construct & easy to use, clean & maintain
- Equipped with a condenser to condense vapor so that evaporation is speeded up, inconvenience is reduced & equipment is used for solvents other than water
- A receiver & vacuum can be fitted to the condenser to permit operation under reduced pressure & temperature

Disadvantages

❖Natural convection only

❖All the liquor is heated all the time

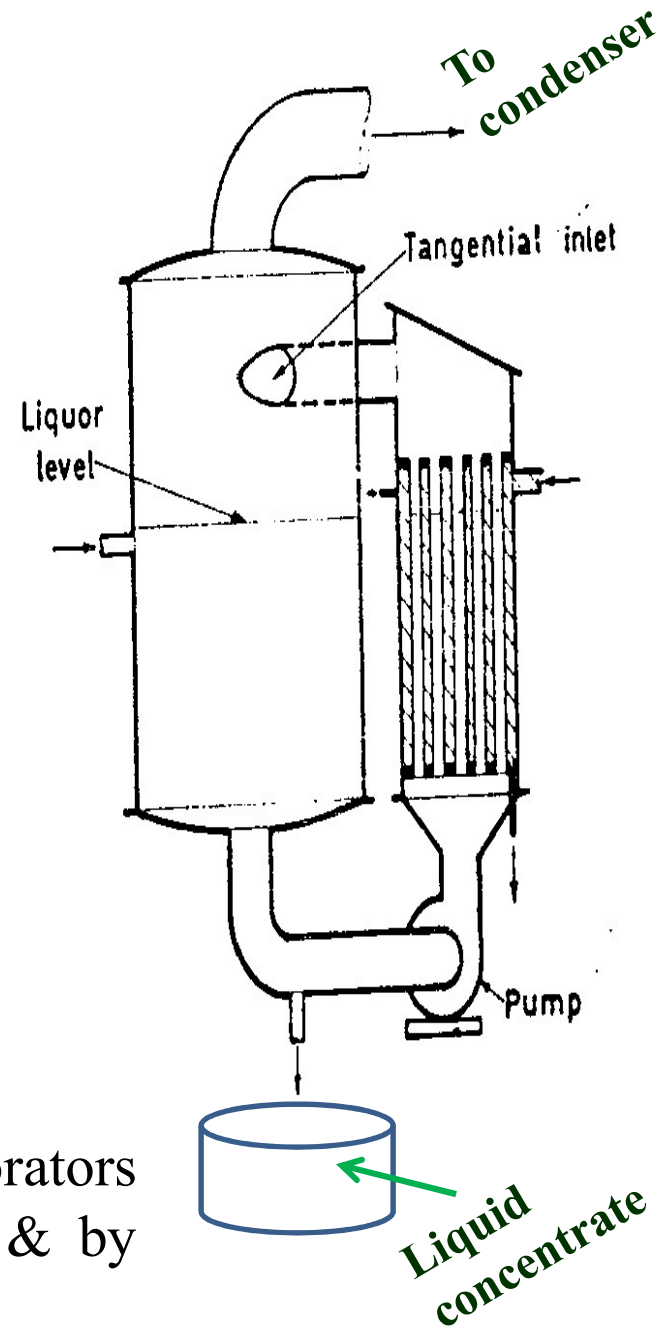
❖Limited heating surface



Evaporating stills

2. Forced circulation evaporators

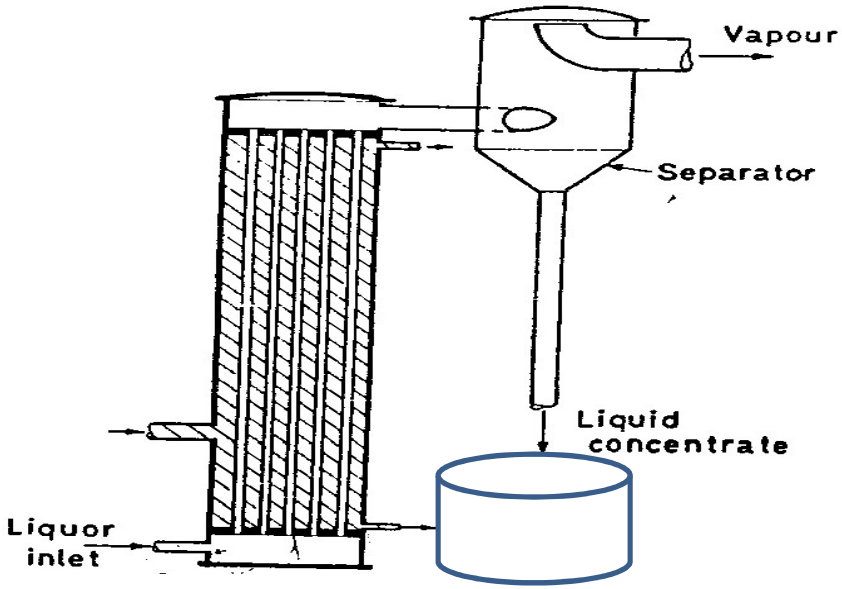
It is a modified form of natural circulation evaporator such as evaporating pan or still since it is equipped with mechanically operating paddle or propeller agitator or pump that rapidly moves viscous liquor there by minimizing deposition of solids on heating surface and improving heat transfer. It can be operated under reduced pressure & temperature with rapid evaporation rate, hence it is suitable for thermolabile materials such as insulin & liver extracts



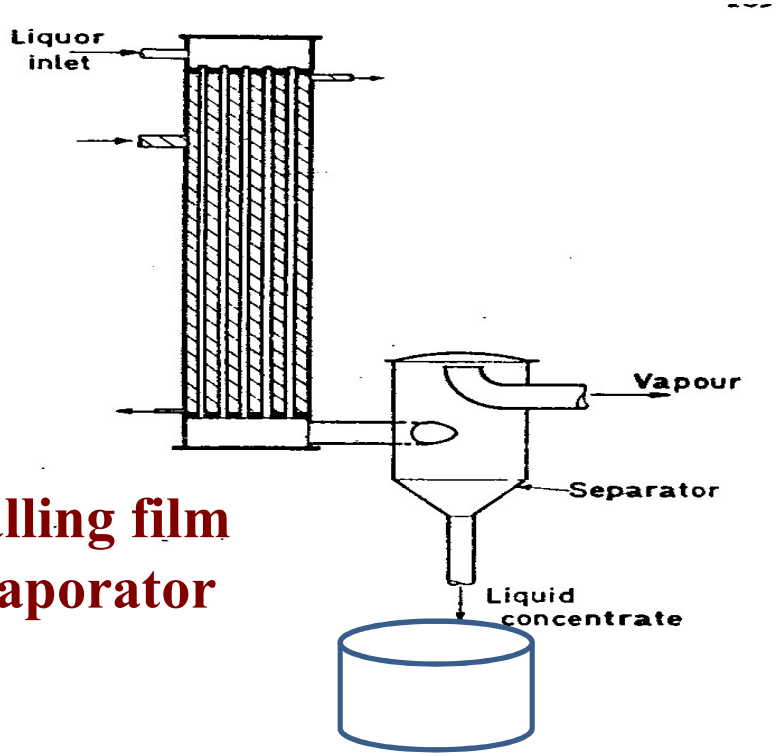
Note: Both Natural & forced circulation evaporators are operated by boiling the liquor in a vessel & by escaping vapour as bubbles from the liquor bulk

3. Film evaporators

The liquor is introduced at the bottom of the tube, a film of liquid forms on the walls of the tube [which is about 7m in length & 50 mm in diameter & rises up the tubes at a velocity of 6-7m/sec, hence the name climbing film evaporator. At the upper end, the mixture of vapor & concentrated liquor enters a cyclone separator, the vapor passing on to a condenser & concentrate to a receiver



Climbing film evaporator



Falling film evaporator

Advantages

- Very high film velocity reduces boundary layers to a minimum giving improved heat transfer
- Long narrow tubes, about 50 mm in diameter provides large area for heat transfer
- Because of increased efficiency of heat transfer, a small temperature difference is sufficient,
- Suitable for heat-sensitive materials since it has short heating time, large heating surface & fast evaporation rate
- Mixture of liquid & vapor enters cyclone separator at high velocity which improves separation efficiency and makes the method suitable for that foam

Disadvantages

- Very expensive to manufacture, difficult to clean and maintain
- Has critical feeding rate; if too high makes insufficiently concentrated liquor & if too low, film cannot be maintained & dry patches may form on the tube wall.

Distillation

- Separation of constituents of a mixture which have appreciably different vapor pressures

Pharmaceutical uses

- ❖ Extraction of volatile active principle from vegetable drugs
- ❖ Isolation of volatile substances from their less volatile solvents
- ❖ Separation of one liquid from non-volatile impurities
- ❖ Separation of a liquid from at least one liquid with which it may be miscible, partially miscible or immiscible

Types of distillation

- Simple distillation
- Fractional distillation
- Steam distillation

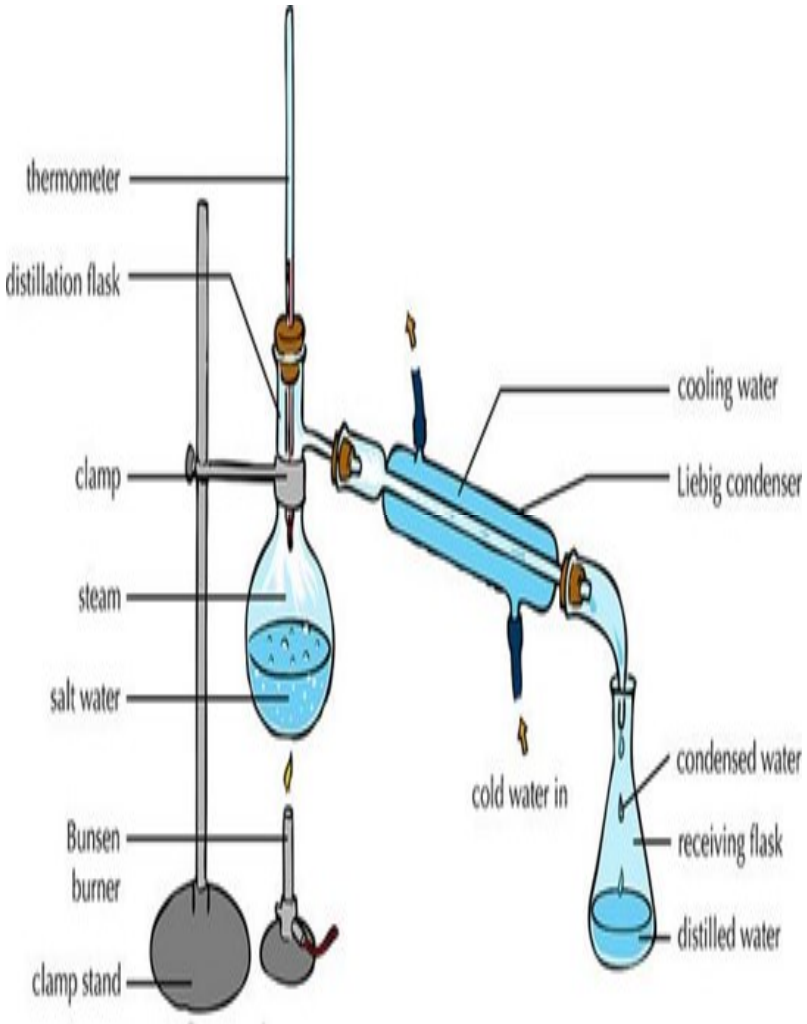
Simple distillation

- Process of converting a liquid into its vapor , then recovering the purified liquid after condensation
- Used for isolation of a liquid from non-volatile solids

Example:

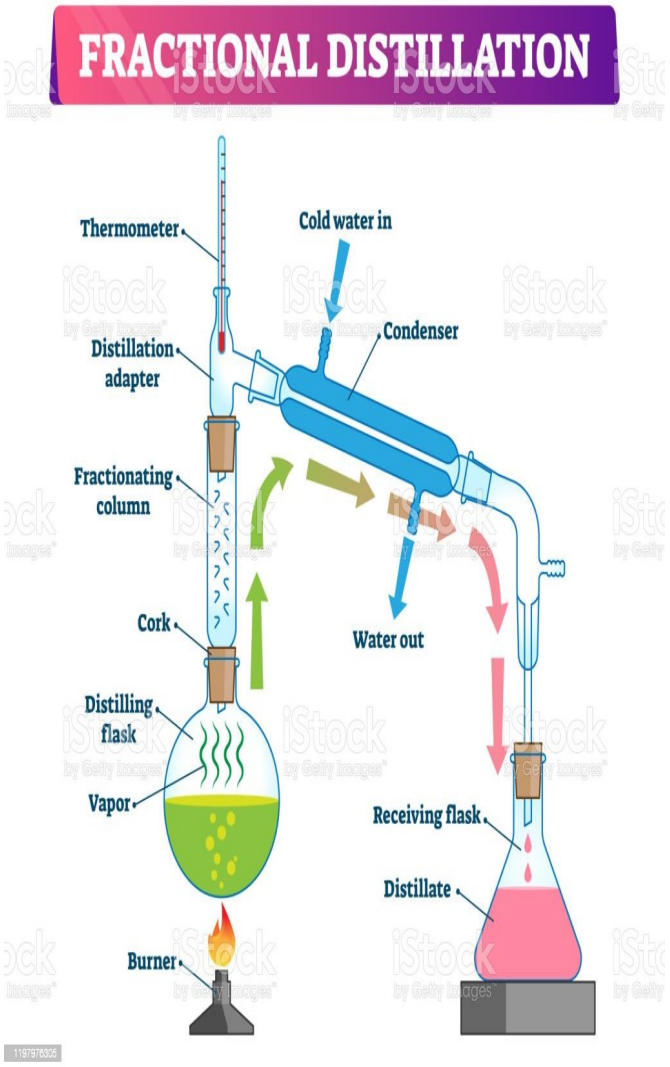
- Preparation of distilled water
- Recovery of alcohol in the preparation of dry extract

- Components of simple distillation apparatus includes Still, Condenser, and Distillate receiver



Fractional distillation[or Rectification]

- Used to isolate miscible volatile liquids having different boiling points
- Possibility of separation of two liquids depends on the effect each has on vapor pressure of each other
- Liquid with relatively higher vapor pressure effect will be first isolated & received as a distillate
- Differs from simple distillation as it allows partial condensation of vapor in fractionating column via w/h vapor should first pass prior to reaching condenser
- Fractionating column let ascending vapor come in contact with condensing vapor & both return to the still enriching the vapor in more volatile component



Steam distillation

- Used for distillation of water-immiscible liquids having high boiling points such as turpentine, aniline
- Separates oils heavier or lighter than water
- Isolates oils having specific gravity equal to one
- Needs collection of distillate containing both water & such oil. Then ,the oil will be later extracted using readily volatile solvent
- Used for determination of volatile oils in drugs
- Used for the production of water for injection(WFI)

Filtration

Filtration: Removal of solid particles from a fluid by passing the fluid through porous medium & retaining solids deposits

Clarification: Removal of visible solid particles from the liquid so that it still contains solids not exceeding 1%.

Filter cake: Residues collected on filter medium

Filtrate or effluent: Clear liquid passing via filter

Filter aids: Insoluble substances added to the liquid slurry to reduce resistance of filter cake by preventing solid from contacting & plugging supporting filter medium & to increase filtration by forming more porous & less compressible cake

Materials used as filter aids	Composition	Advantage	Disadvantage
Carbon	Carbon	Filtering strong alkaline solutions	Coarse grade only & Expensive
Cellulose	Cellulose	High purity & Excellent chemical resistance	Expensive
Diatomaceous earth	Silica	Wide range; Used for very fine filtration	Slightly soluble than diatomites in acid & alkali
Asbestos	Aluminosilicate	Good retention on coarse screens	More soluble than diatomites in acid & alkali
Perlite	Silica & Aluminosilicate	Wide range; not capable of finest retention	More soluble than diatomites in acid & alkali

Objectives of filtration

- Collecting filtered gas or liquid as a product after removing solid impurities from fluids
- Collecting solid deposits as ultimate products as in the case of recrystalization that aimed at collection of purified crystals

- **Factors affecting rate of filtration are expressed based on Darcy's law**:

$$\textbf{Filtration rate} = \frac{dV}{dt} = \frac{K * A * \Delta P}{\eta * L}$$

Where,

- V= volume of filtrate
- t= filtration time
- K= constant for filter medium & cake
- A= area of filter medium
- ΔP= change in pressure across filter medium
- μ = viscosity of filtrate
- L=thickness of cake & filter medium

Discuss impact of each factors on filtration rate !!!

Types of filtration

I. Based on preparation to be filtered

1. Solid/liquid filtration
2. Solid/gas filtration
3. Liquid/gas filtration

II.Based on degree of filtration

1. Sterile filtration
2. Non-sterile filtration

Pharmaceutical application of Solid/liquid filtration

- Improvement of appearance of liquid pharmaceuticals
- Sterilization of thermo-labile liquid products
- Microbial detection in liquid preparation
- Removal of fine colloidal matters of vegetable drugs from solvent extraction
- Recovery of desired solids following crystallization process
- Removal of potential irritants from ophthalmic solutions

Pharmaceutical application of Solid/gas filtration

- Removal of suspended solid particles from air to be used for processing equipments such as FBD, spray dryer, film coating m/c, bottle cleaning equipments
- Removing particulate matters from exhaust air prior to venting to atmosphere[exhaust air from Fluidized Bed Dryer (FBD), coating machine]

Pharmaceutical application of liquid/gas filtration

- Removing entrained oil or water droplets during manufacturing of compressed air that can be used in a number of pharmaceutical processes such as film-coating spray guns, bottle-cleaning equipment and fluid energy mills

Sterile filtration

- Used to clarify & sterilize parenteral pharmaceuticals
- Pore size of membrane filter is 0.2 &/or 0.45 µm [microbial proof filters]
- Completely removes particles of 0.3 µm
- Applicable to both thermo-labile & thermo-stable preparations

Note:

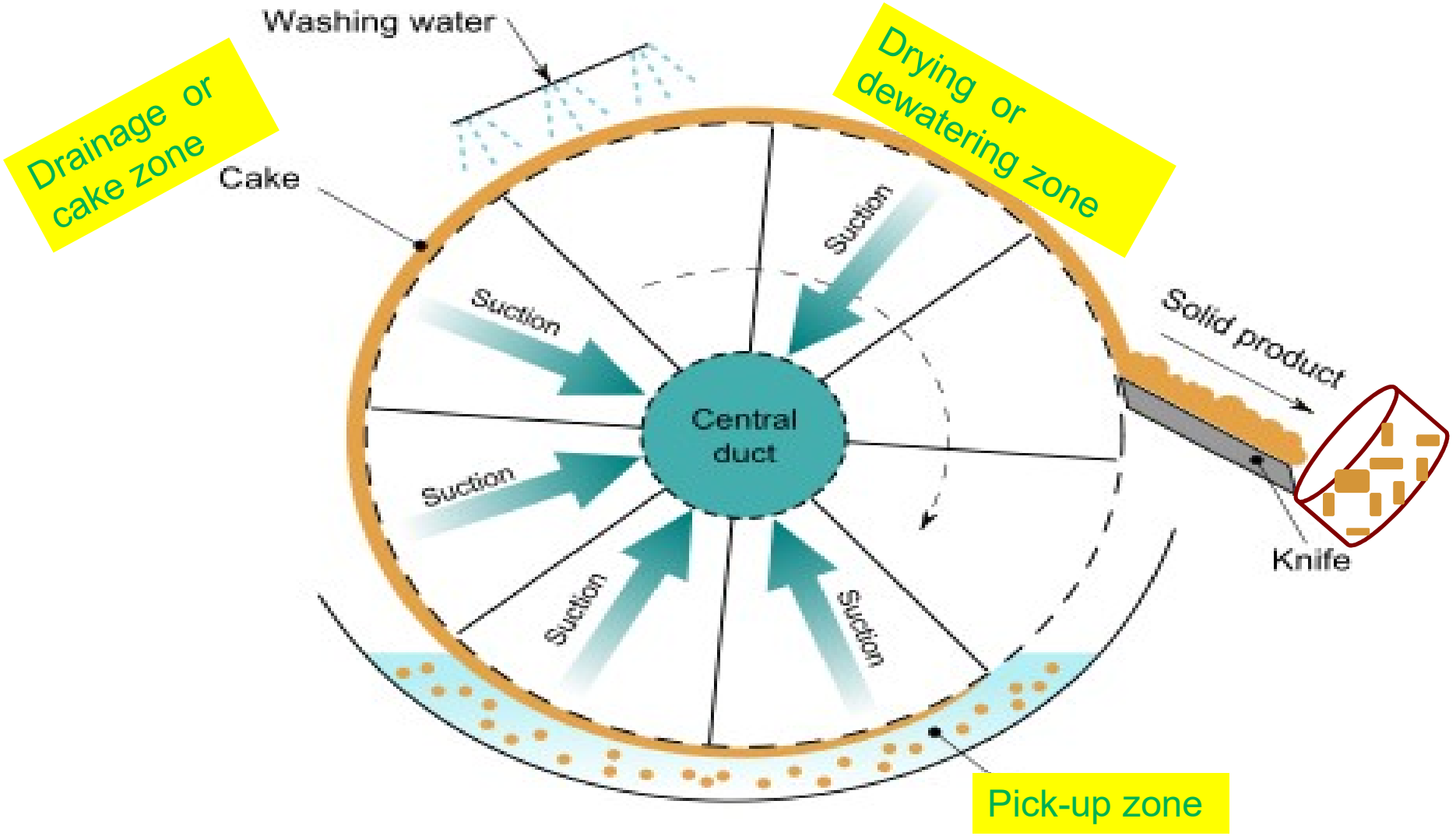
- Pore size of filtration medium must be lower than size of microorganisms unless it is adsorptive.

Filter types

- Gravity filter: Open system that operates with water column pressure only
- Pressure filter: Closed system that operates under pressure from a pump
- Vacuum filters such as rotary vacuum filter or Continuous rotary filters

Rotary vacuum filter

- Has two concentric cylinders with the annular space between them divided into a number of septa by radial partitions.
- Outer cylinder is perforated & covered with a filter cloth
- Each septum has a radial connection to a complicated rotating valve
- Cylinder rotates slowly in continuously agitated slurry and a vacuum applied to the segments draws filtrate into septa, depositing cake on the filter cloth
- Filter cake is continuously removed by scraper blade, aided by compressed air forced into septa, thus enabling continuous operation using concentrated slurries for long period of times



Rotary vacuum filter

Parameters to be considered during filter selection

- Ability to trap solid particles
- Minimum resistance for the filtrate to flow through
- Resistance to chemical attack
- Minimum cost
- Durability
- Sufficient mechanical strength to withstand filtration pressure
- Be inert
- Adsorb negligible amounts of dissolved material

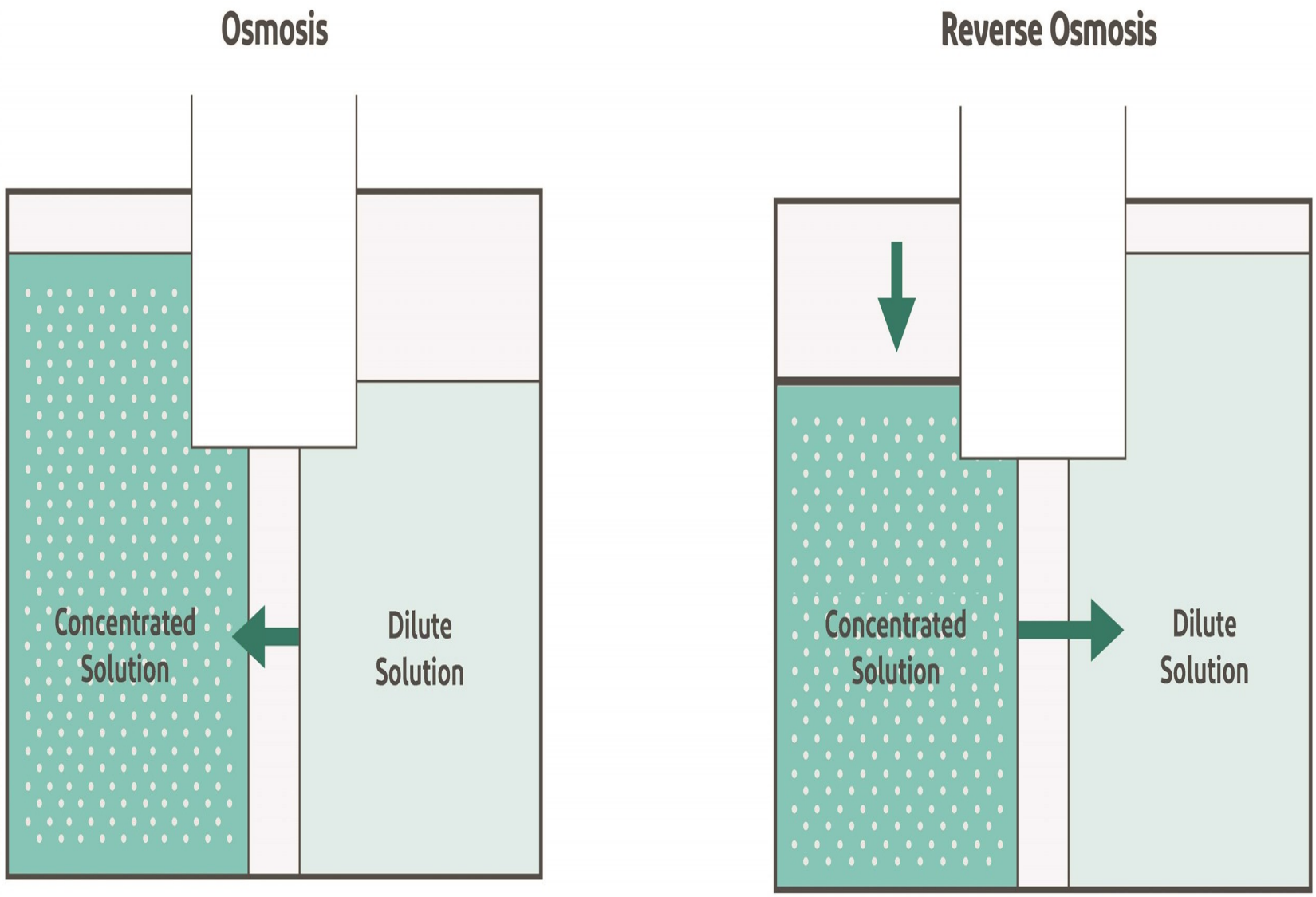
Reverse Osmosis

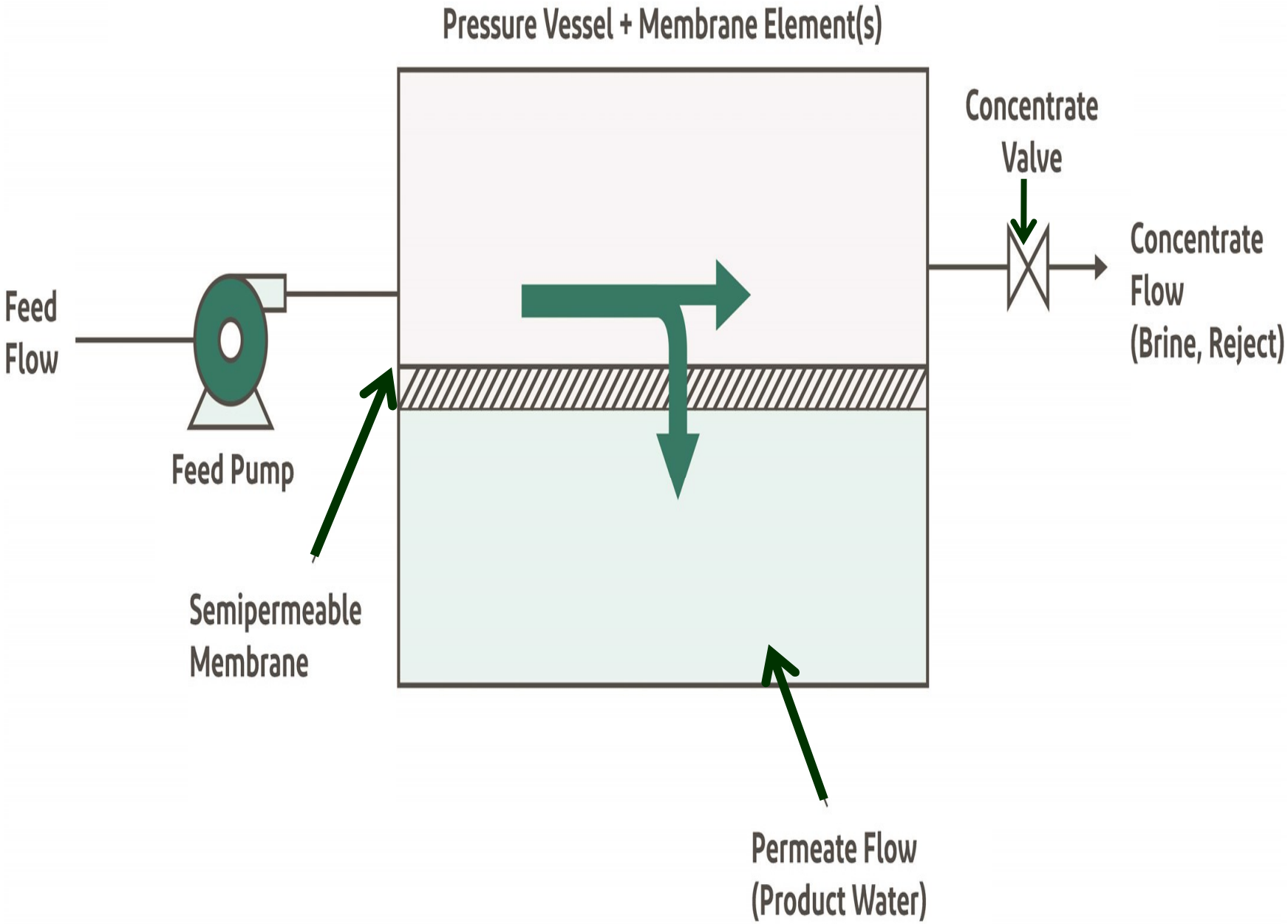
What is Reverse Osmosis[RO]?

- It is a technology that is used to remove a large majority of contaminants such as dissolved salts, organics, bacteria and pyrogens, etc from water by pushing the water under pressure through a semipermeable membrane
- RO demands applying pump generated pressure that is greater than naturally occurring osmotic pressure in order to desalinate (demineralize or deionize) water in the process, allowing passage of pure water molecules but blocking passage of majority of contaminants via semipermeable membrane

Types of water obtained after fed water is passing through RO system:

1. Permeate or product water is water from which majority of contaminants [95% to 99.9% of dissolved salts] are removed by RO membrane
2. Concentrate, reject, or brine water is water that contains all of the contaminants that are unable to pass through the RO membrane


Osmosis
Concentrated Solution
Dilute Solution
Reverse Osmosis
Concentrated Solution
Dilute Solution


Pressure Vessel + Membrane Element(s)
Concentrate
Valve
Concentrate
Flow
(Brine, Reject)
Feed
Flow
Feed Pump
Semipermeable
Membrane
Permeate Flow
(Product Water)

Centrifugation

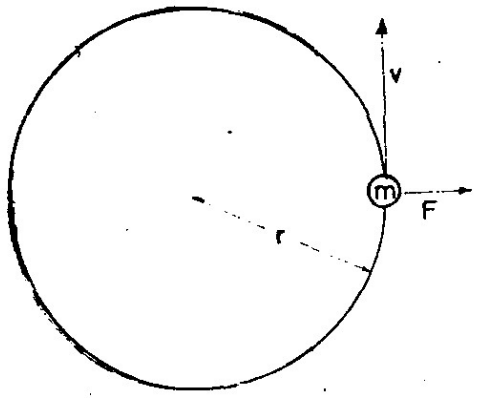
How it is conducted?

- Usually, a given particle settles under gravitational force at a fixed maximum rate
- to increase the settling rate, we replace the force of gravity by a much stronger centrifugal forces
- More effective than gravity separators because they will separate fine drops and particles and are much smaller in size for a given capacity.

Principles of Centrifugation

It is operated using centrifugal force which is measured as a product of gravitational force and centrifugal effect [the № of times the centrifugal force is greater than the gravitational force]

Centrifugal effect is obtained as follow:



- F=centrifugal force $=mv^2/r$ and
- G= Gravitational force = mg
- $F/G = mv^2/mgr = v^2/gr$ but $v=2\pi rn$
- $F/G = (2\pi rn)^2/gr = 4r(\pi n)^2 = 2d(\pi n)^2/g$
- F/G = Centrifugal effect $=2.013dn^2$
- Where m & V= mass & velocity of the body, r= rotational radius(m) and n= rotational speed expressed as s^{-1}

Note: If it is vital to increase centrifugal effect, use centrifuges of same size but higher rotational speed, rather than using larger centrifuge at same speed of rotation

Reason: Centrifugal effect is directly proportional to the diameter, but is proportional to the square of the speed of rotation

Example:

1. Compute centrifugal effects for centrifuges of 1 m in diameter but with rotational speeds of 15 & 30 s^{-1}.

   [Answer: centrifugal effects = 453 & 1,812, respectively]

2. Compute centrifugal effect for a centrifuge 100mm in diameter and operating at a rotational frequency of 400 s^{-1}

   [Answer: centrifugal effect = 32,208]

3. Find centrifugal force for each case and compare their relative separation effects if applied to same homogenous liquid preparation

Types of centrifuge

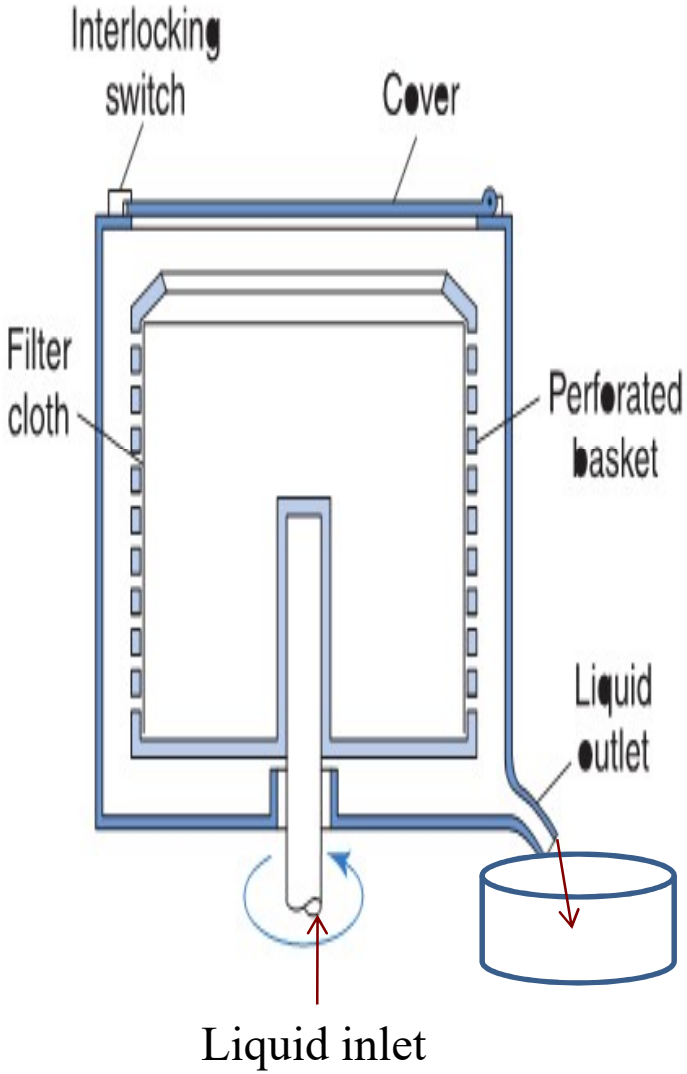
A. Laboratory tabletop centrifuge

B. Industrial centrifuges

1. Perforated-basket centrifuges (centrifugal filters)
2. Tubular-bowl centrifuges (centrifugal sedimenters)

1. Perforated-basket centrifuges (centrifugal filters)

- Operates on separation of solid- liquid mixtures having large sized bulk materials, at very small speed with low centrifugal effect
- Consists of a stainless steel perforated basket lined with a filter cloth
- Product enters centrally & is thrown outwards by centrifugal force & held against filter cloth
- Filtrate is forced through the cloth and removed via the liquid outlet; the solid material is retained on the cloth
- Used for example to remove precipitated proteins from insulin

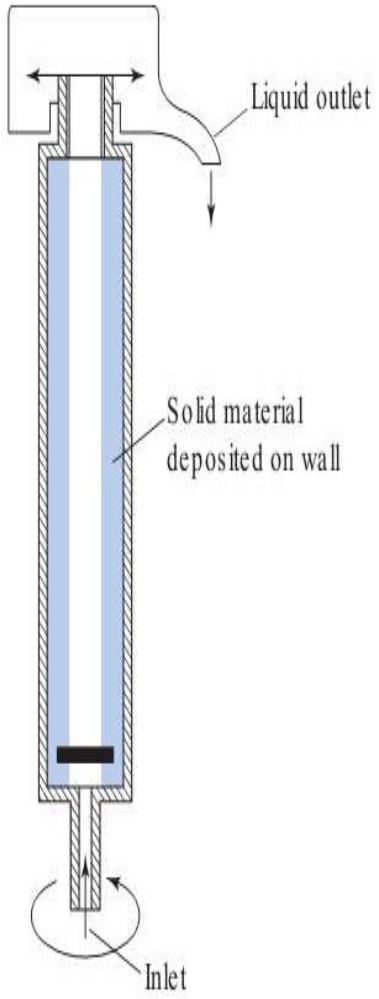


2. Centrifugal sedimenters or Tubular-bowl centrifuges

- Acts on both liquid/liquid and solid/liquid mixture consisting of very small sized particles that necessitates a centrifuge having high centrifugal effect with small diameter but operating at very high speed
- Consist of a rotating cylindrical 'bowl‘
- Product enters at the bottom and centrifugal force causes deposition of solids on the wall as it passes up the bowl & overflowing of liquid from the top
- Can be adapted to separate immiscible liquids

Used for:

- Removal of compressible solids that easily block filter medium
- Separation of blood plasma from whole blood
- Separation of different particle size fractions
- Examining stability of emulsions



Uses of centrifuge

- Separate solid substances from mother liquor

Example:

- ❖ Formed elements from plasma
- ❖ Viruses
- ❖ Bacteria- enzyme preparation
- ❖ Crystalline drugs of different density
- ❖ Purification of starch
- ❖ Insulin preparation

- Separate immiscible liquids

Crystallization

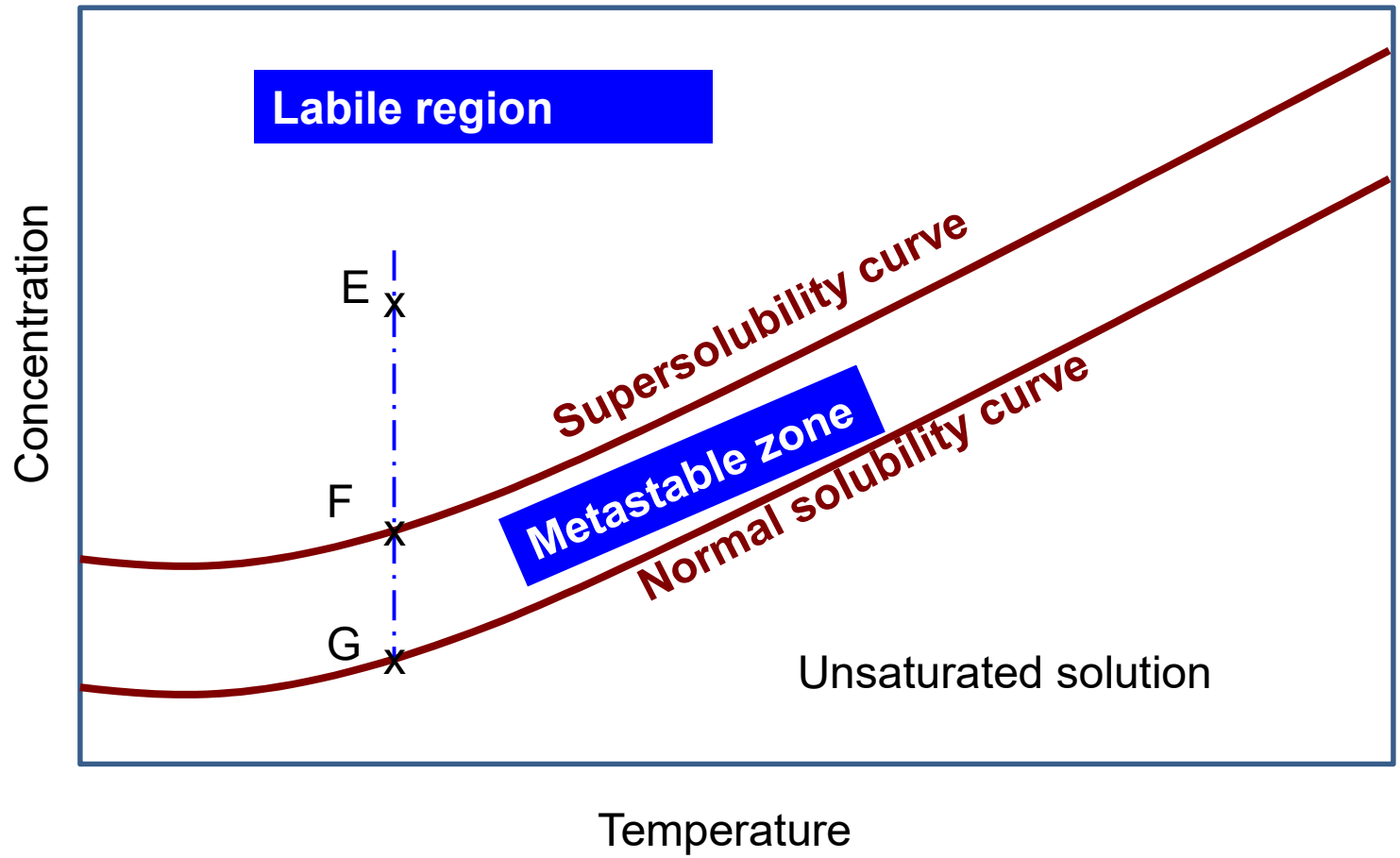
What is crystallization ???

- Process of forming crystal of definite shape from its melt or solution
- Formation of solid particles within a homogenous phase
- Applied to production of crystals from vapor, liquid melt, or solution
- Process that involves reversal of changes which occurs when solid melts or dissolves
- Pure crystalline solid can be separated from vehicle by centrifugation, filtration or drying
- Understanding crystallization processes is vital for :
  - » rational formulation and process development
  - » Physicochemical stability of pharmaceutical products

Mechanism of crystallization

- A solution must be saturated before any solid mater can crystallize out
- If temperature of such solution is lowered or its solvent is allowed to evaporate then surplus solid crystallize out
- Formation of crystal from solution involves two steps:
    1. Creation of crystalline nuclei
    2. Crystal growth

- The driving force for nucleation & subsequent crystal growth is supersaturation of solution as shown by solubility curve below



Note

- In the metastable region no appreciable spontaneous nucleation, however, there is copious spontaneous nucleation above the supersolubility curve
- A solution of compositions ‘E’ will spontaneously crystallize & solution concentration falls to that given by normal solubility curve, at the prevailing temperature at point ‘G’
- A solution compositions represented by point F in the metastable zone remain unchanged unless seeds are added & when nucleation occurs concentration drop to point ‘G’

How nuclei originate?

1. Spontaneously by cooling solution in labile region
2. Deliberate seeding with minute crystals
3. Fortuitous seeding by crystals left from previous batch
4. Attrition or stirring of existing crystals giving rise to fragment that act as seeds

Note:

- Slow cooling of supersaturated solution form few nuclei & large crystals while continuous stirring & rapid cooling form a large number of nuclei & a crop of small crystal
- Presence of impurities inhibit nucleation
- Crystal growth in suspension is undesirable

Reason:

- Hard cake difficult to redisperse can be formed
- Crystal growth enhance grittiness of topical preparation

Fractional crystallization/ Recrystalization

- Useful for purification of crystalline substances from a solvent in which impurities are more soluble than the substance being purified

Steps

1. Select suitable solvent for the impure substances
2. Dissolve impure substance near its boiling point
3. Filter the solution while hot to remove impurities
4. Cool the effluent at low temperature to form crystals
5. Collect the crystal from supernatant solution
6. Wash crystal to remove adhering solution and dry
7. Repeat steps 1-5 sequentially, to obtain pure crystals
8. Finally conduct physical tests [m.p, b.p, density, solubility, crystal morphology] & chemical tests [assay, specific test for purity].

A. Solve the following problems [Quiz-2]

1. The ratio of viscosity of fluid to the product of fluid density & pipe diameter is 0.85 while Reynold's number for same fluid is 6000. Then, determine (a) optimal flow velocity of the fluid (b) average velocity at which laminar flow occurs(c) average velocity at which turbulent flow occur
2. Determine as to which centrifuge should have better fractionation capacity if rotational radius & rotational speed of centrifuge-A are 0.8m & 10 rpm while that of centrifuge-B are 2.4 m & 20 rpm. respectively.

B. Write true or false and give reason

1. A system of fluids subjected to natural & forced convections have same rates of heat transfer
2. The design of an evaporator has no impact on concentrating effect of solution
3. The yield of active principles obtained following leaching and extraction methods have identical quality

Unit 3:Particle size and powder technology

3.1. Introduction to solid state properties

3.2. Particle size analysis

3.3. Particle size reduction

3.4. Particle size separation

3.5. Mixing

3.6. Powder flow

3.1. Introduction to solid state properties

[Crystal & Crystal habits, Polymorphism, Hydrates and solvates, amorphous state, Surface energy and powder sorption]

- Solid state is vital for a variety of reasons: Drug particle size & morphology, polymorphism, solvation or hydration affect filtration, flow, tableting, capsule filling, dissolution and bioavailability
- A crystal is an orderly arrangement of molecules that permits optimal attractive interactions between adjacent molecules within solid & creates diffraction pattern we observe, as X-rays are reflected from regular array of atoms
- Solids with lower melting point requires less energy to disrupt the interactions within them & hence have greater solubility
- Solids with higher melting point require more energy to disrupt interactions within them and has poorer solubility

Examples

Melting point and water solubility of structurally similar drugs		
Compound	**Melting point (°C)**	**Water solubility**
Acetylsalicylic acid (aspirin)	135	1 g/300 mL
Salicylic acid	157–159	1 g/460 mL

- Crystalline habit refers to visually inspected shape of drug crystal
- A drug's crystal habit may be described as needle-like (acicular), columnar, pyramidal, prismatic, plate-like and tabular
- Shape of drug particle is important to its flow, compressibility, dispersibility and aerodynamic properties, as shown below:

Effect of crystal habit

1. **Ease of injection of suspension:** Plate-like crystals are easier to inject through a fine needle than are needle-like crystals
2. **Flow properties of the drug in the solid state**

Equidimensioned granules/particles have good flow while irregular particles have poor flow properties

3. **Ease of compression of a tablet:** Plate-like crystals of tolbutamide cause powder bridging in the hopper and capping problems during tableting while other crystal habits of tolbutamide are free from such problems

Factors affecting crystal habits

Conditions of crystallisation

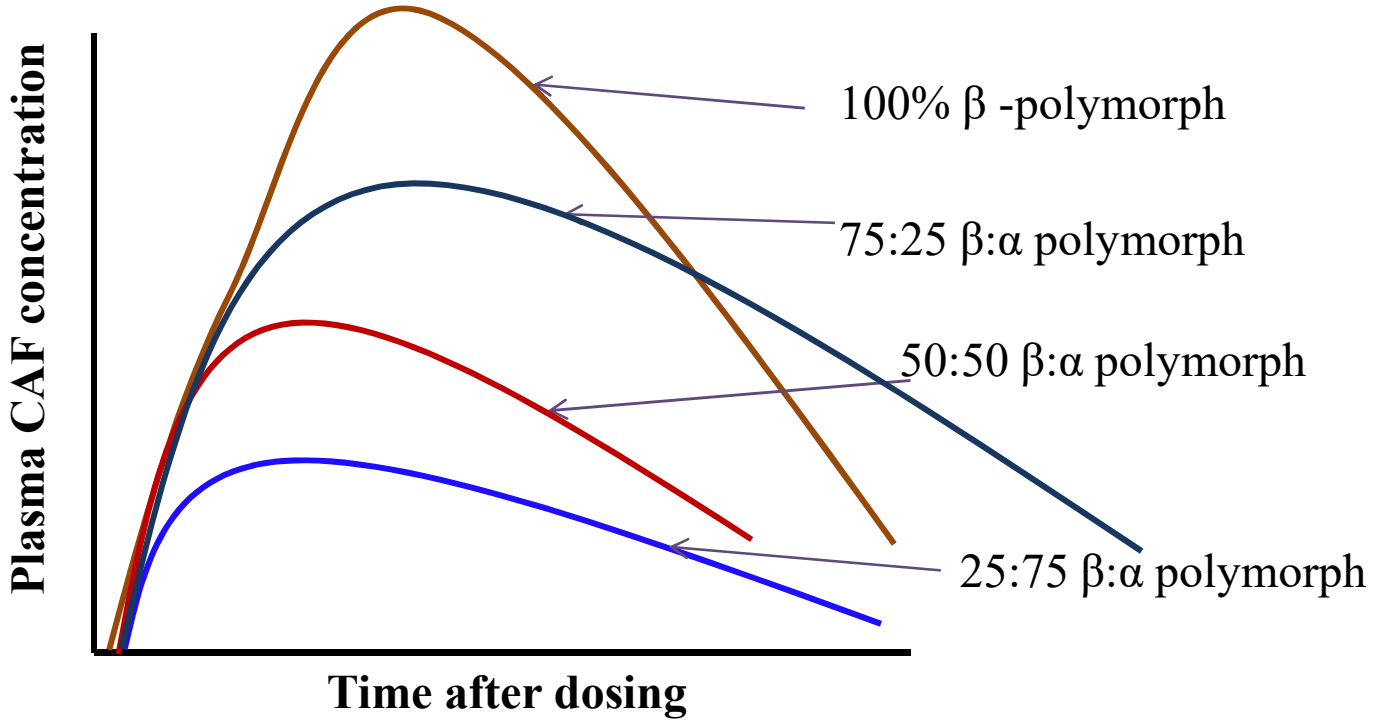
- Temperature
- Concentration
- Presence of impurities
- Solvent used

Example:

Ibuprofen crystallised from hexane as elongated needle-like crystals have poor flow properties while crystallisation from methanol produces equidimensional crystals with better flow properties and compaction characteristics, making them more suitable for tableting

Polymorphism & bioavailability

- Polymorphism refers to existence of a drug in different crystal habits [forms]. About 36% of drugs exhibit polymorphism.
- Polymorphic drug crystals usually exist in two crystal forms known as stable and metastable
- The stable and metastable forms have different physical properties [solubility, melting, X-ray diffraction, density, dissolution rate, etc]
- Metastable forms have relatively larger bioavailability than the stable form during production. Why??
- The metastable crystals are converted to stable form during shelf-life of the dosage form, thus decreasing bioavailability below therapeutic level
- Therefore, polymorphism can influence melting point, solubility, dissolution rate and bioavailability of a drug, and processing properties such as powder flow and compressibility



Comparison of mean blood serum levels after the administration of CAF- palmitate suspensions using varying ratios of the stable (α) & metastable (β)

Note: Polymorphism can complicate preparation of suspensions because as the drug moves in & out of solution it will ultimately re-form in the most thermodynamically stable & least soluble form.

Solvates [Pseudopolymorphism]

- They are orderly arrangements of drug molecules formed by trapping solvent molecules in their crystalline lattice.
- If the solvent used is water, the crystal is called **hydrate**, if other solvents are used, the crystal lattice is called **solvate** [Eg: Ethanolate if ethanol is used]

Is it recommendable to use organic solvent to form pharmaceutical solvate? Why??

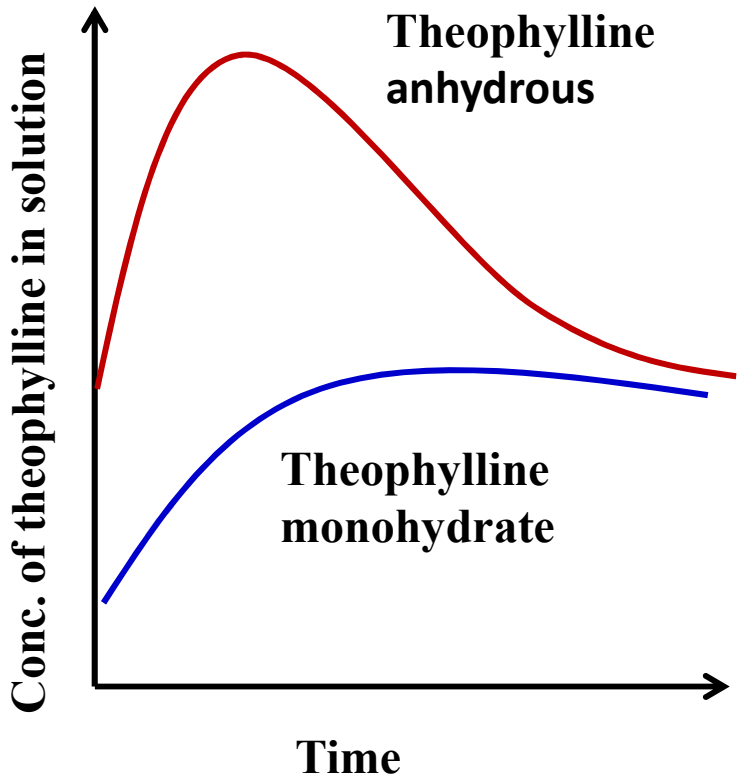
- Entrapment of water molecule is often in an exact molar ratio with crystallizing drug molecules, hence number of water molecules per drug molecule will be mentioned in the name of the solid
- Monohydrate, dihydrate, trihydrate,etc will have one, two, three, etc molecules of water for each molecule of the crystallizing material, respectively

Example:

- ✓ Theophylline monohydrate
- ✓ Amoxicillin trihydrate
- ✓ Magnesium sulfate heptahydrate

❖ The most usual situation is for anhydrous form of the drug to have faster dissolution rate than the hydrate

Reason: Water could hydrogen bond b/n two drug molecules & tie the lattice together giving a much stronger, more stable lattice & hence a slower dissolution rate



Dissolution of theophylline monohydrate rising to an equilibrium solubility, compared with that for theophylline anhydrous which forms a supersaturated solution with a peak over twice that of the dissolving hydrate, before crystallizing to form true equilibrium solubility

Amorphous state

- Amorphous solids have no orderly arrangement of molecules within the solid; they are simply a pile of molecules with minimal interactions between molecules that can be easily disrupted by solvent.
- Thus, amorphous form of a drug always have a lower melting point and a better solubility than the crystalline form(s) of same drug.
- Amorphous solids may be formed when a drug solution is cooled so rapidly that solute molecules lose mobility before assuming their lattice positions as occurs in freeze drying procedures

- Amorphous solids are generally porous and low density, rendering them susceptible to sorption of vapor from the atmosphere and subsequent chemical or microbial instability
- In general, amorphous solids have very different physical properties from crystal form of same drug

Note: Polymorphs & solvates of the same drug have different physical properties causing problems in their formulation, analysis & absorption

pharmaceutical implications of polymorphism

A. Formulation problems

- Polymorphs with certain crystal habits may be difficult to inject in suspension form or to formulate as tablets
- Transformation between polymorphic forms during storage can cause changes in crystal size in suspensions and their eventual caking.
- Crystal growth in creams as a result of phase transformation can cause the cream to become gritty.
- Changes in polymorphic forms of vehicles such as theobroma oil, used to make suppositories, could cause products with different and unacceptable melting characteristics.

B. Analytical issues

- Difficulties in identification arise when samples that are thought to be the same substance give different infrared spectra in the solid state because they exist in different polymorphic forms
- Change in polymorphic form can be caused by grinding with potassium bromide when samples are being prepared for infrared analysis
- Changes in crystal form can be induced by solvent extraction methods used for isolation of drugs from formulations prior to examination by infrared spectroscopy – these can be avoided by converting both samples and reference material into the same form by recrystalization from the same solvent

C. Bioavailability differences

- Different polymorphic forms of a drug has impact on its bioavailability

Examples

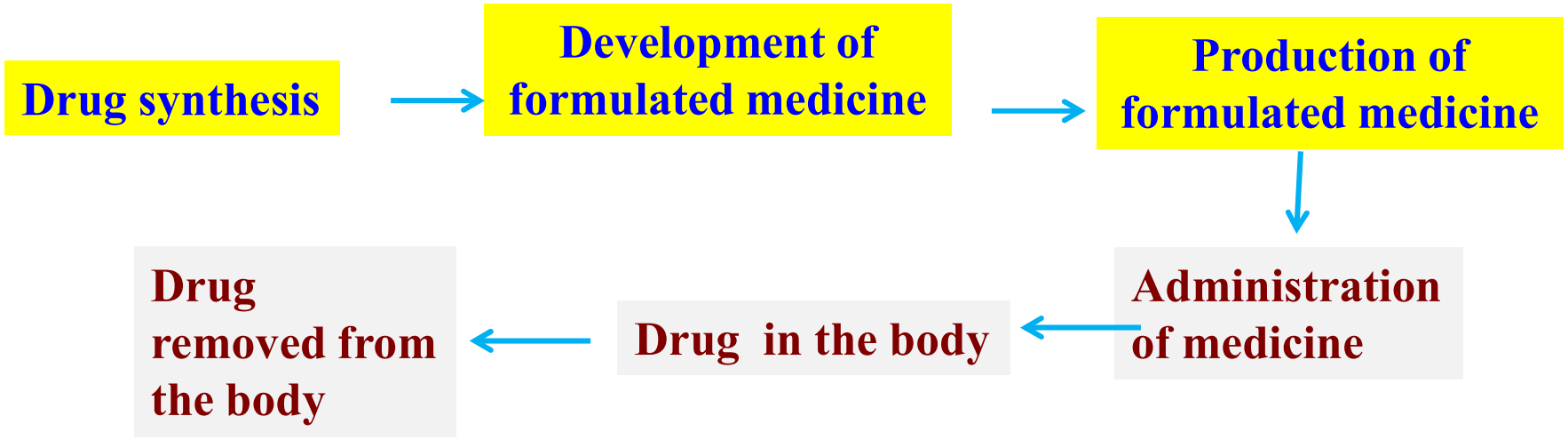
- Chloramphenicol palmitate where polymorph A of the three polymorphic forms is poorly absorbed
- Amorphous form of warfarin will have better water solubility than crystalline form, that is, amorphous form will dissolve more rapidly & to a greater extent.
- Use of amorphous form could increase amount & rate of warfarin absorbed resulting in a greater anticoagulant effect & possible bleeding & bruising in patients who switch from crystalline form

3.2. Particle size and particle size analysis

A. Particle size

- Dimensions of particulate solids are important in achieving optimum production of efficacious medicines
- Particle size influences production of formulated medicines [eg.: tablets & capsules]. How?
  - Mass of drug incorporated into tablet or capsule is influenced by volumetric fill which in turn depends on powder flow and compressibility characteristics
  - Poor powder flow reduce content uniformity of medicine
  - Powders with different particle sizes have different flow & packing properties, that alter the volumes of powder during each encapsulation or tablet compression event

Lifetime of a drug



The lifetime of a drug outlined above shows that a knowledge and control of particle size is important both for the production of medicines containing particulate solids and in the efficacy of the medicine following administration.

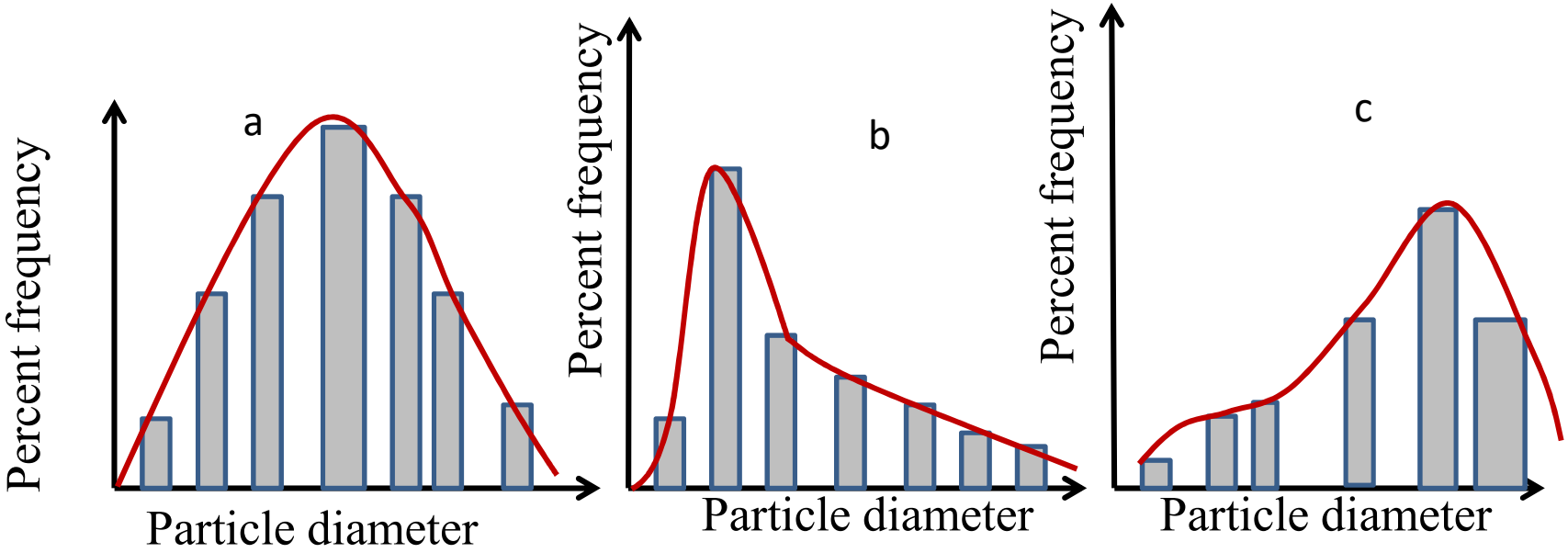
Impact of particle sizes in determining dosage forms to be manufactured	
Dosage form	**particle size range (µm)**
Ophthalmic suspensions	≤10
Oral suspensions	10–*50*
Parenteral suspensions	0.5–*25*
Parenteral dispersions for intravenous use (emulsions, liposomes, nanoparticles) USP	0.1–*0.5*
Aerosols for the lung	1–*5*
Tablets and capsules, immediate release	≤50
Topical aerosols	50–*100*
Topical emulsions	≤50
Topical suspensions	10–*50*

B. Particle size analysis

i. Particle size distribution

- Population of particle consisting of spheres or equivalent spheres with uniform dimensions is monosized & its characteristics can be described by a single diameter or equivalent diameter
- However, most powders contain particles with a large number of different equivalent diameters
- Particle size distribution can be studied using histogram or frequency polygon
- Monosized particles have normal distribution while particle with different size may be positively or negatively skewed

- Not all particle populations are characterized by symmetrical normal size distributions & frequency distributions of such populations exhibit skewness
- Positively skewed particle size distribution shows existence of more larger particles while negative skewness corresponds to more of small sized particle distribution



Frequency distribution curves corresponding to (a) normal distribution, (b) positively skewed distribution and (c) Negatively skewed distribution

Particle size analysis methods

1. Sieve method
2. Sedimentation method
3. Microscope method
   - ❖ Light microscope
   - ❖ Scanning electron microscope[SEM]

Particle size separation : Sieve method

The mesh is vibrated at high speed, often by an electrical device.

Particle size: Sedimentation method

$$\frac{dV}{dt} = \frac{D^2[\rho_p - \rho_m]g}{18\eta}$$

$$D = \sqrt{\frac{18\eta h}{tg[\rho_p - \rho_m]}}$$

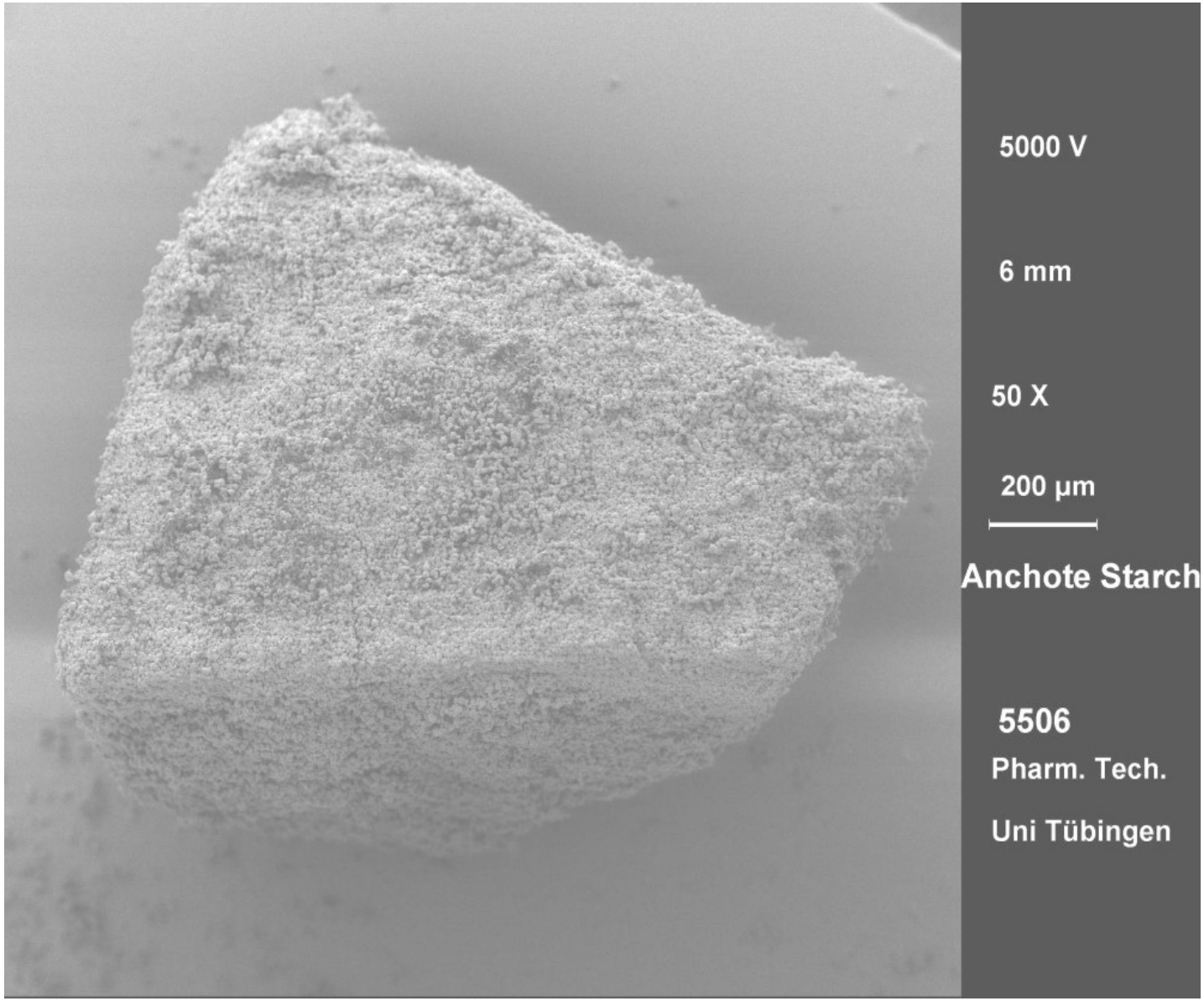
Where

v= h/t

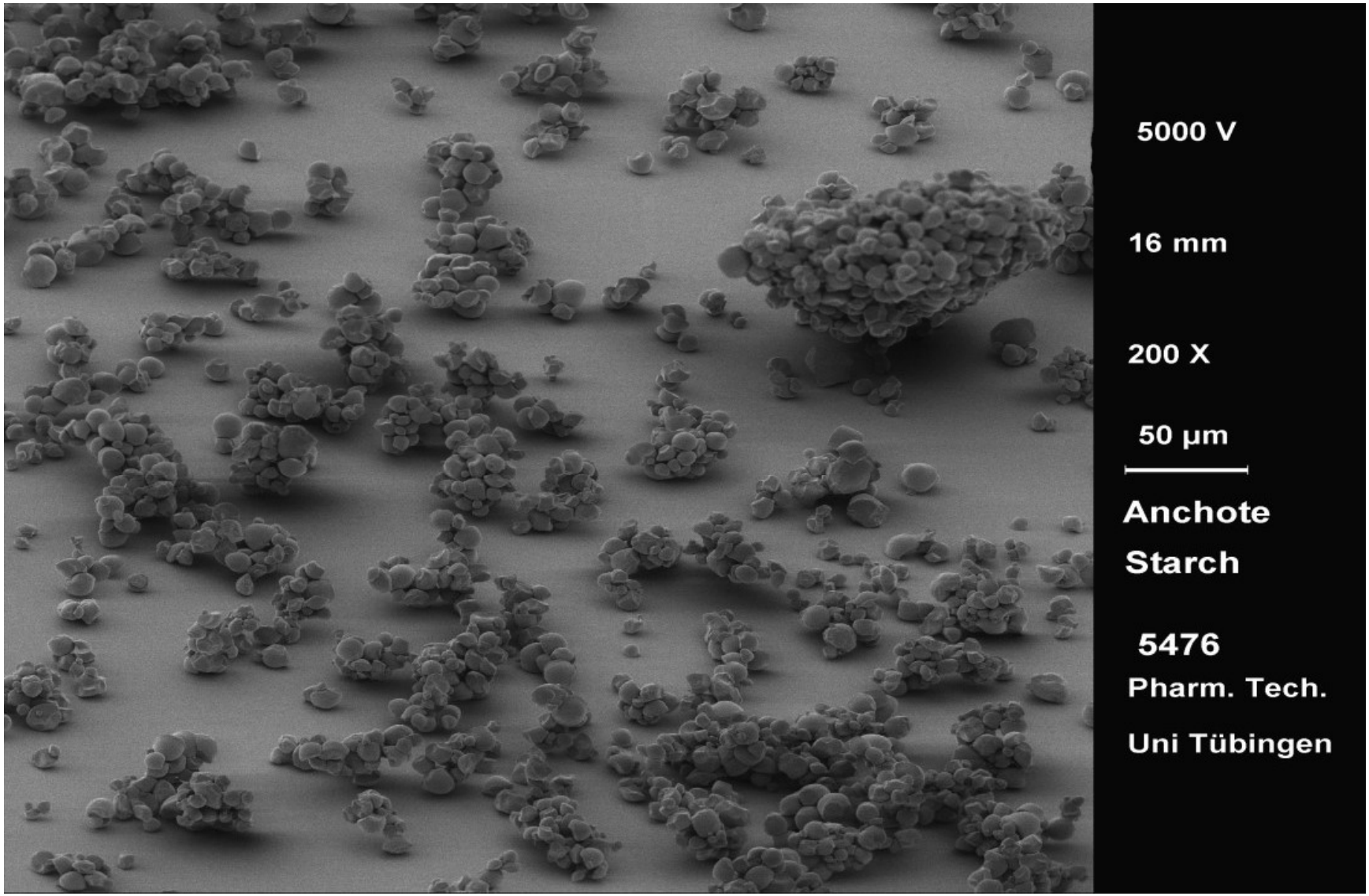
h= height of a sediment

t= time for sediment , 'h' to occur

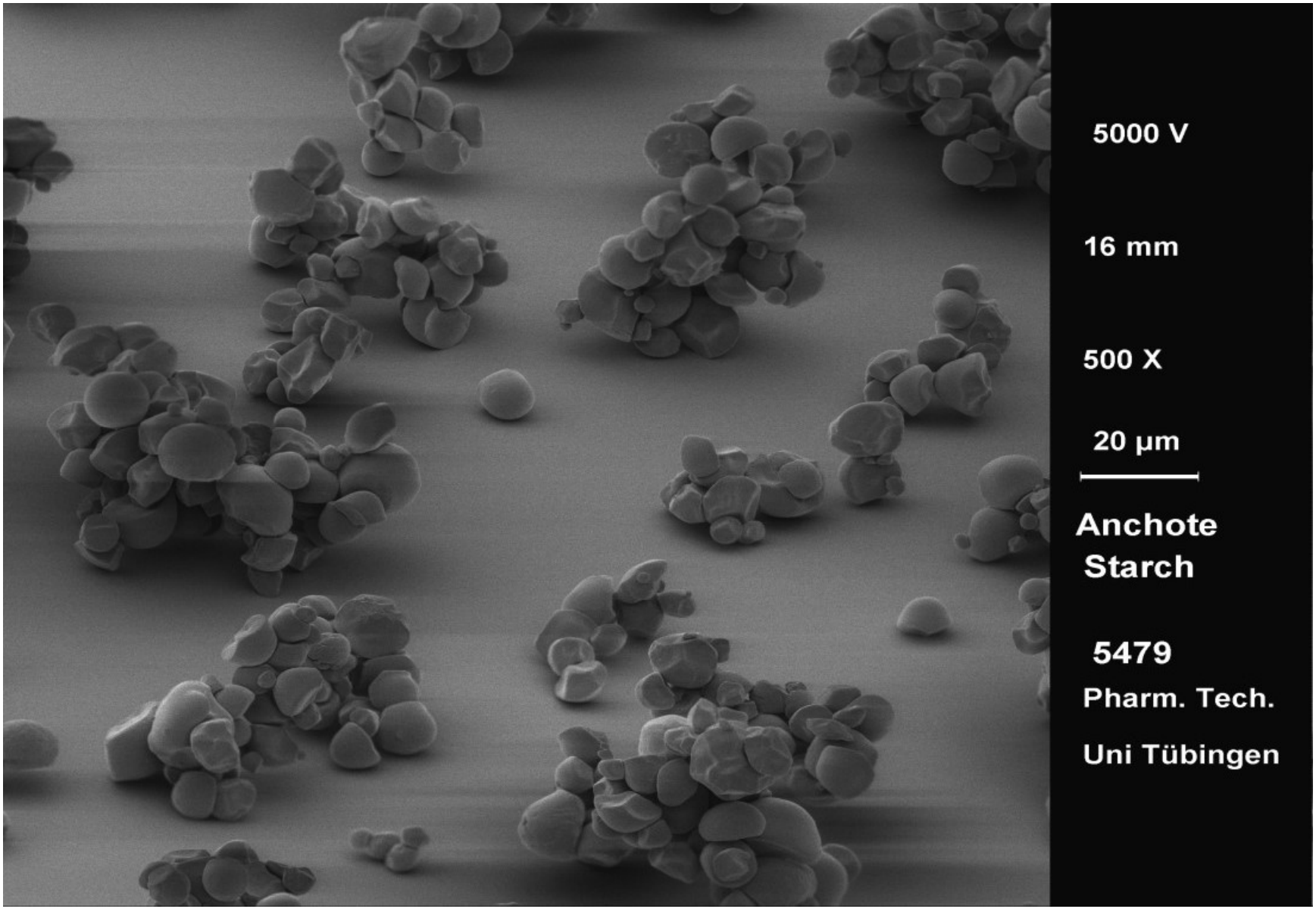
Particle size analysis method : Scanning electron microscope



Scanning electron microscope[SEM]



Scanning electron microscope[SEM]



Particle size reduction/Comminution

Comminution: Reduction of sizes of materials in to smaller pieces, or to powders. It includes wide variety of operations like cutting, chopping, crushing, grinding, milling, micronizing, and trituration.

Objectives of size reduction

- to produce smaller particles
- to facilitate mixing of powders
- to increase surface area
- to increase adsorptive properties
- to reduce bulk volume of material
- to improve transportation

Mechanisms of size reduction

Cutting: Using sharp blade such as cutter mill on large scale & Knife cutter or Root cutter on small scale

Compression:

- Crushing of material by applying pressure
- Used to extract fixed oil from seeds

Example:

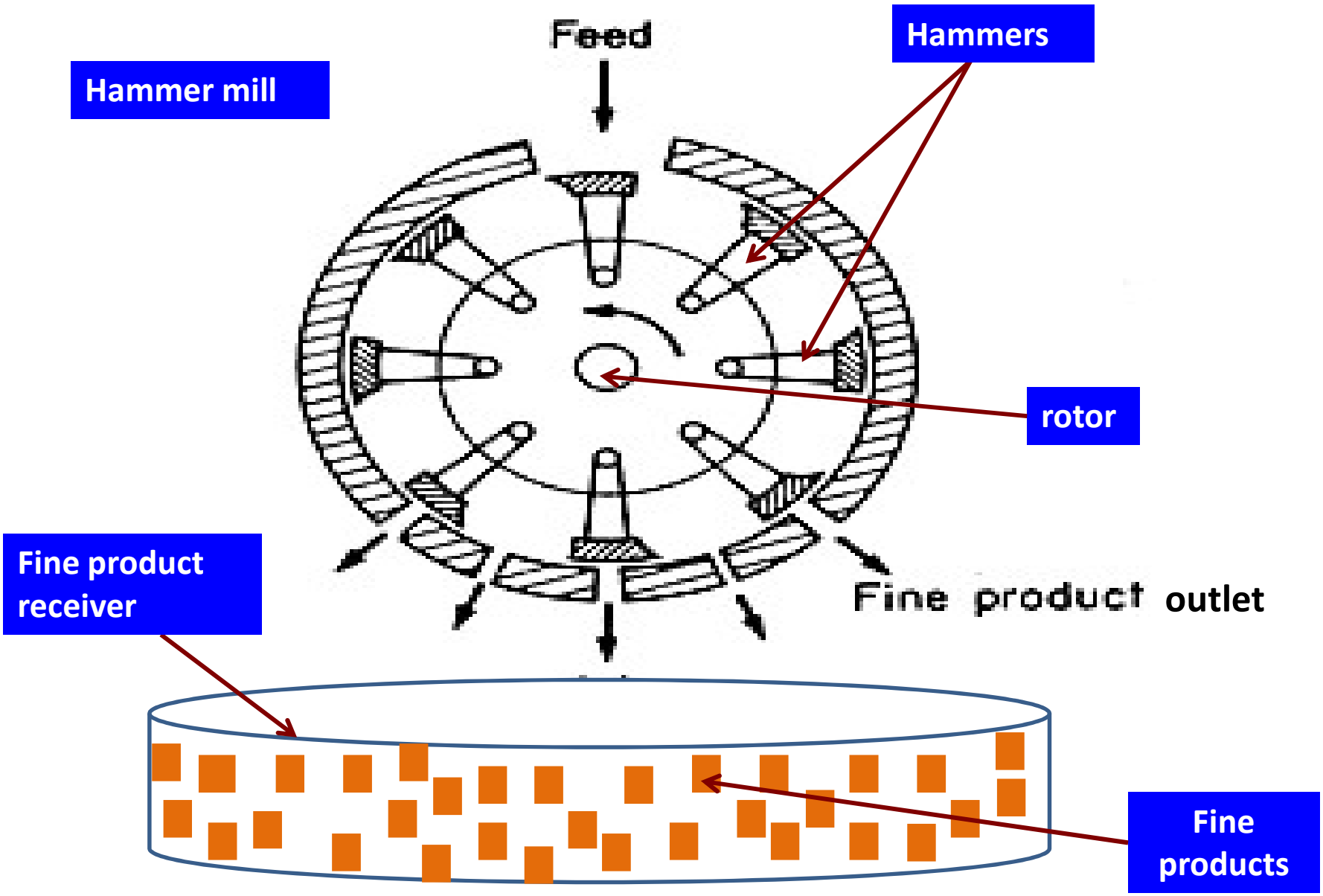
- On small scale: pestle and mortar
- On large scale: Roller mill, Jaw crusher

Impact

- Stationary material is hit by an object moving at high speed or
- When the moving particle strikes stationary surface.
- used to prepare granules for tableting

Example:

- On small scale: Hammer, mortar and pestle
- Industrial scale: Hammer mill


Hammer mill
Feed
Hammers
rotor
Fine product outlet
Fine product receiver
Fine products

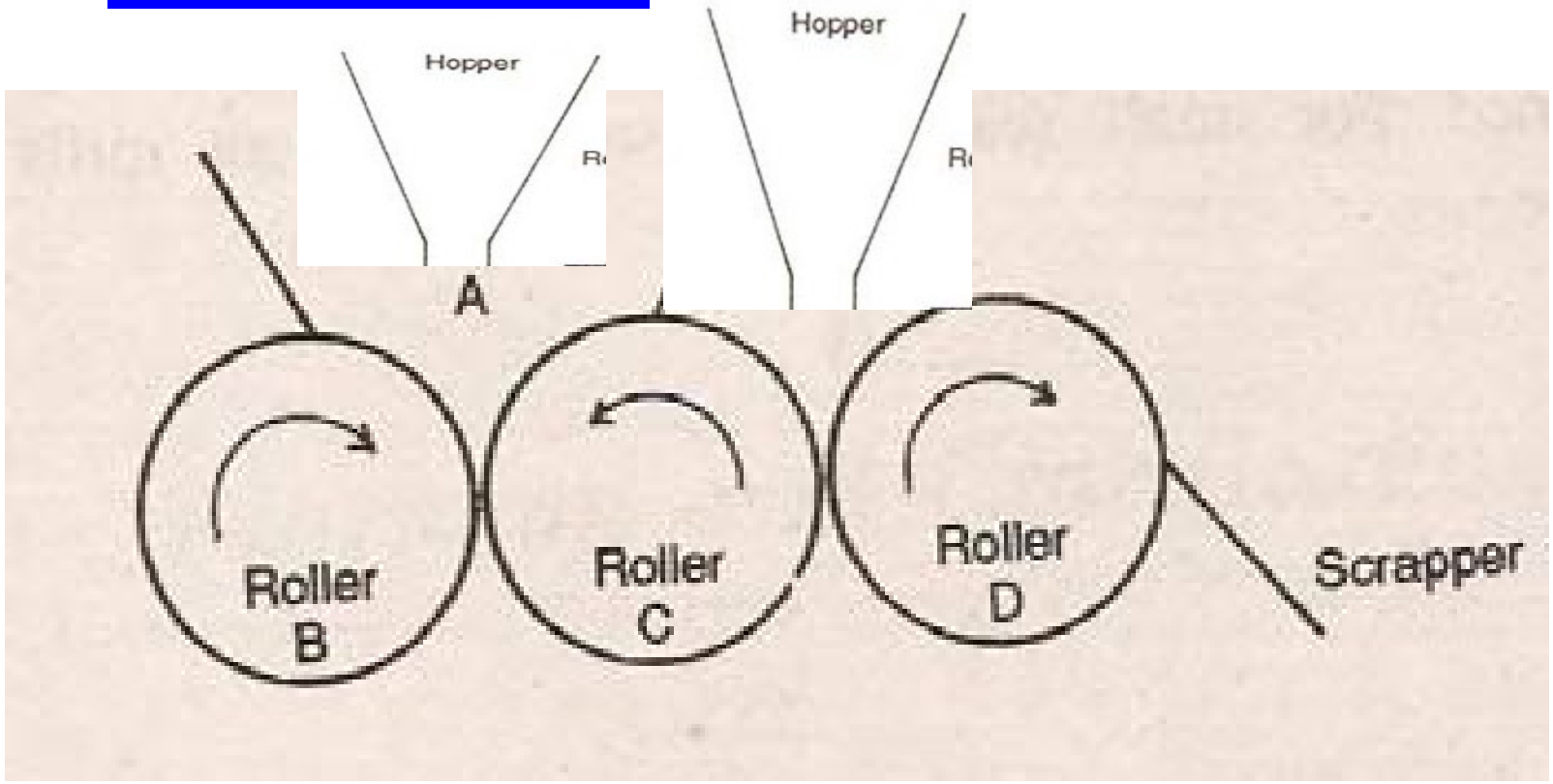
Attrition

- By applying pressure as in compression, but the surface are moving relative to each other, resulting in shear forces which break the particles
- Shearing / friction

Example:

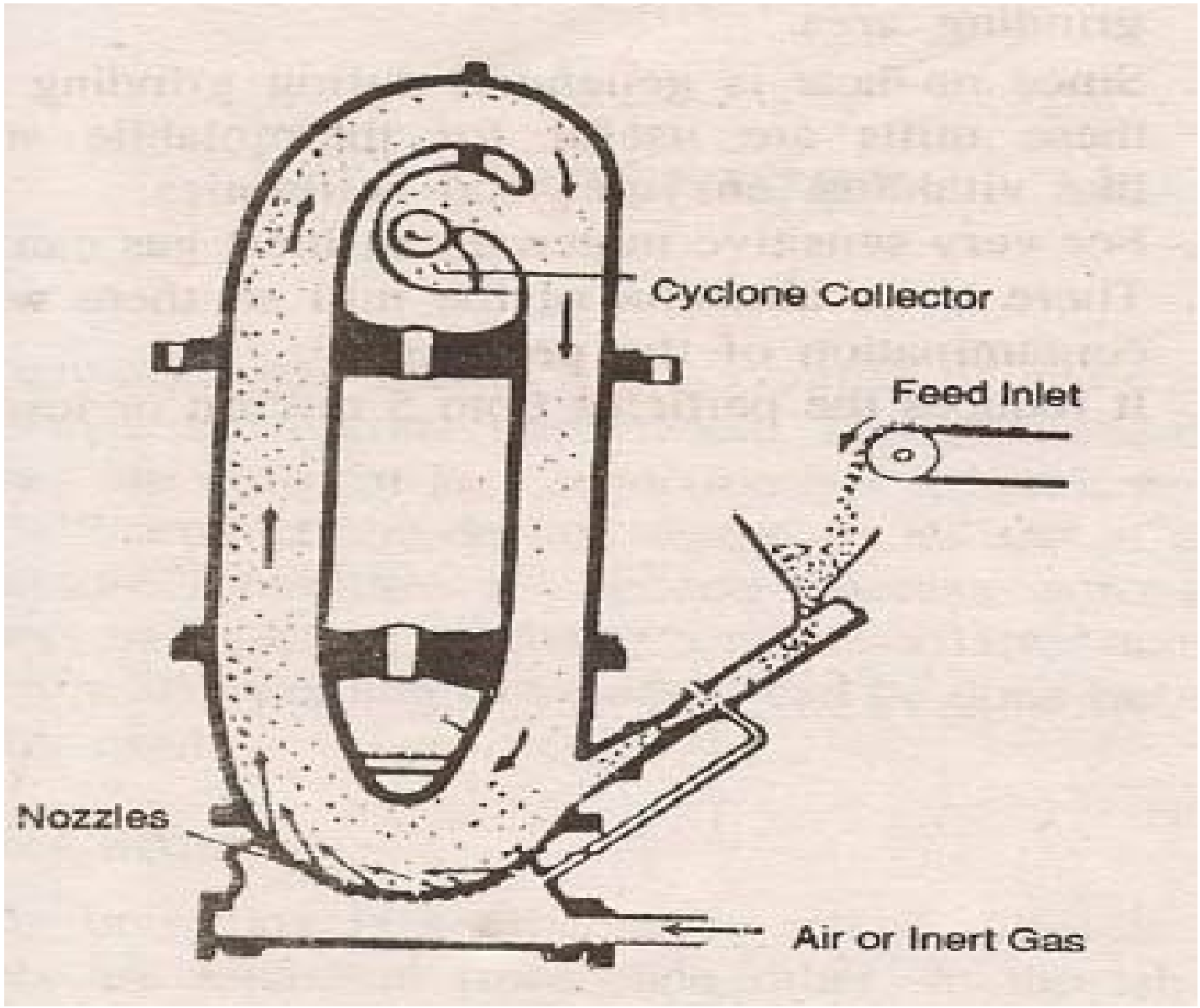
- In laboratory : Lab. Based roller miller
- Roller mill on large scale

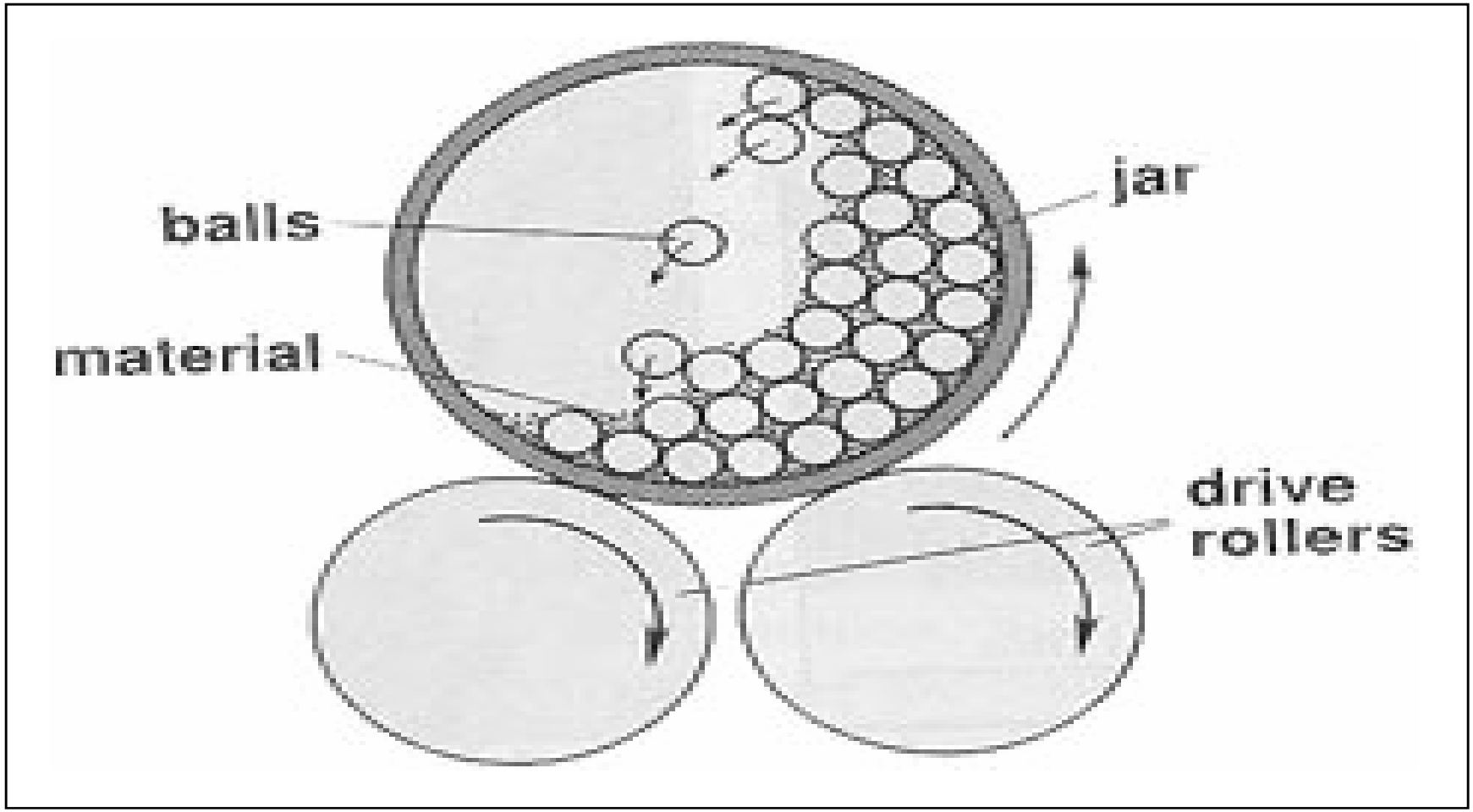
Triple roller mill



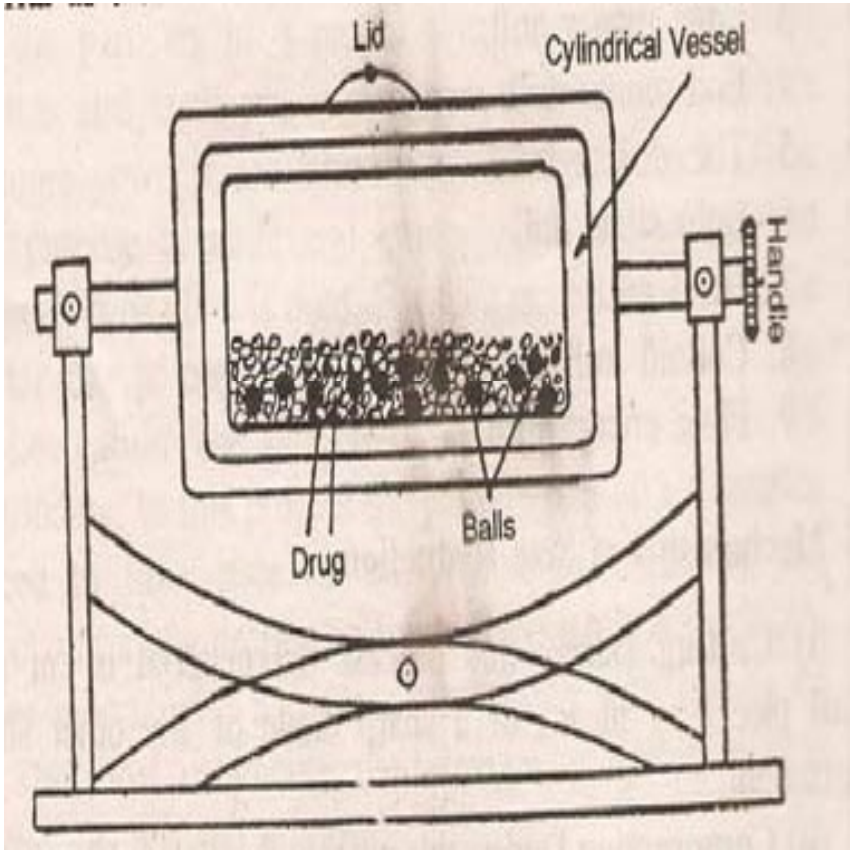
Fluid energy mill

- Air, is injected at high pressure through nozzles at the bottom of the loop, giving rise to a high velocity circulation in a very turbulent condition
- Solids are introduced into the stream
- High degree of turbulence, impact and attrition forces occur between the particles
- A classifier is incorporated in the system, so that particles are retained until sufficiently fine


Cyclone Collector
Feed Inlet
Nozzles
Air or Inert Gas


balls
material
jar
drive
rollers

Ball mill



Note:

Combined impact and attrition observed in Ball mill and Fluid energy mill

- In ball mill, the particles receive impacts from balls and pebbles, and are subjected to attrition as the balls slide over each other.
- In fluid energy mills, the impacts and attrition occur between rapidly moving particles

Summary of types of mils		
Name of the mill	**Mechanism of action**	**Uses**
Hammer mills	Impact	Almost for all the drugs
Roller mills	Attrition &compression	Soft materials
Colloid mills	Impact & attrition	Almost for all the drugs
Ball mill	Impact & attrition	Brittle drugs
Fluid energy mill	Impact & attrition	Moderately hard and friable materials

Factors influencing choice of machinery for Size Reduction

- Degree of Comminution required[Size Reduction Range]
    - Roller mill……175-100,000 micrometer
    - Hammer mill……30-10,000 micrometer
    - Ball mill ……..1-125 micrometer
    - Fluid energy mill……5 micron or less
    - Colloidal mill…….less than 1 micron
- Nature of raw material
- Nature of product & equipment

Selection of size reduction methods		
Degree of size reduction	**Typical methods**	**Examples**
Large pieces	Cutter or Compression mills.	Root, peel
Coarse powders	Impact mills	Liquorices, Cascara
Fine powders	Combined impact and attrition mills	Belladonna
Very fine powders	Fluid energy mills	Vitamins, Antibiotics

Pharmaceutical application of size reduction

- Increase surface area
- Enhanced solvent penetration, dissolution & extraction rates
- Improved therapeutic effectiveness[eg: Griseofulvin]
- Facilitate homogeneous mixing of solid ingredients
- Optimize tableting by improving granules flowability
- Avoids grittiness of topical preparation
- Enhance rate of drying by improving heat & mass transfer
- Improves drug bioavailability

Particles size separation

Size separation is usually an integral part of size reduction in industrial pharmacy

Reasons:

- Machines used for size reduction do not necessarily produce particles of uniform size
- Particle size distribution control within a narrow size ranges demands sifting of size-reduced material
- Desired fractions are finally mixed, if necessary, to get a powder having average particle size

- Control of particle sizes & size range in pharmaceutical industry is very important

  Reason: particle sizes have different impacts on processing of pharmaceutical dosage forms & their therapeutic effectiveness

Example

Particle sizes affect:

- Speed of sedimentation & degree of redispersibility from suspension [$V = 2r^2(\rho_s-\rho_m)g / 9\eta$] S= solid , m= medium
- Stability of powder mixture
- Flow characteristics of powder
- Mass transfer process [dissolution, extraction, drying, etc]
- Drug absorption from its formulation

- Knowledge and control of size of particles are important in pharmacy and materials science
- Size & hence surface area of a particle can be related to physical, chemical & pharmacologic properties of drugs

Release & dissolution

- Particle size & surface area influence drug release from a dosage form
- Higher surface area allows intimate contact of drug with dissolution fluids in vivo & increases drug solubility & dissolution

Absorption & drug action

The higher the dissolution is the faster the absorption & hence the quicker & greater the drug action

Physical stability:

- Particle size in a formulation influences physical stability of disperse systems such as suspensions & emulsions
- The smaller the size of the particles, the better the physical stability of the dosage form.

Dose uniformity:

- Good flow properties of granules & powders ensures production of tablets & capsules with uniform weight

Objectives of size separation

- To analyze & categorize particles into different particle size range as:
  - Coarse particles
  - Moderate coarse particles
  - Moderately fine particles
  - Fine particles
  - Ultra-fine particles
- To set optimal particle sizes for d/t dosage forms

Example: Large sized particles are used for sustained release while fine ones are for topical formulations

Particle size separation methods

- Several methods are used for particle size separation
- However, **sedimentation** and **sieving** methods are commonly used

Sieving /sifting

- Process by which different grades of powders are separated from each other using set of sieves or different grades of sieves
- Most widely used method for particle size analysis since it is inexpensive, simple & rapid
- Most of the sieves used are of the wire mesh type
- Sieve number indicates number of meshes included in a length of 25.4 mm (1 inch) in each direction parallel to the wires, not the number of wires
- Thus a No. 30 sieve has 30 meshes per inch in each direction [**Sieve number =№ of wires – 1**]

Standards for Powders

- British Pharmacopoeia (BP) has laid down standards for pharmaceutical powders
- B.P. states that degree of coarseness or fineness of a powder is differentiated & expressed by the size of the mesh of the sieve through which the powder is able to pass.
- B.P. specifies five grades of powder, as shown below

First B.P specification for Powders	
Grade of Powders	**Sieve through which all particles must pass**
Coarse	10
Moderately coarse	22
Moderately fine	44
Fine	85
Very fine	120

Short comings of First B.P specification for Powders

- It is an inadequate definition of powders, since particles that pass through a 120 sieve also pass via a 10 sieve
- Hence, the very fine powder meets the same definition as a coarse powder

Remedy

- A limit must be placed on "fines" in the coarser grades of powders by specifying **two sieves** for each powder[BP]:
  - Large sieve size via which all particles must pass
  - Smaller sieve size via which no particles pass

Objective: To obtain a powder with all particles between specified maximum & minimum sizes such that at least 60 % of the powder between those sizes is acceptable

Second B.P specification for Powders		
Grade of Powders	**Sieve through which all particles must pass**	**Sieve through which not more than 40 percent of particles pass**
Coarse	10	44
Moderately coarse	22	60
Moderately fine	44	85
Fine	85	Not Specified
Very fine	120	Not Specified

Sedimentation methods

- Based on the measurement of the rate at which powdered particles settle out from dispersion medium
- Settling is the process by which particulates sediment to the bottom of a liquid
- Settling velocity or fall velocity or terminal velocity of a particle is the rate at which the sediment settles in still fluid. It is sensitive to shape (roundness and sphericity) of particles and to viscosity & density of the fluid. **How ?**
- For dilute suspensions, **Stokes' Law** predicts settling velocity of small spheres in fluid [air or water] as shown below

Stokes' Law:

$$w = 2r^2[\rho_p - \rho f]g/9\eta$$

where ,
w = the settling velocity,
ρ = density (the subscripts ‘p’ & ‘f ’indicate particle and fluid respectively),
g = acceleration due to gravity,
r = the radius of the particle &
η = the dynamic viscosity of the fluid

Mixing

- Aims to treat two or more components, initially in an unmixed or partially mixed state, so that each unit (particle, molecule etc.) of the components lies as nearly as possible in contact with a unit of each of the other components
- Pharmaceutical formulation consists of several ingredients that requires blending to ensure homogenous distribution of the drug molecules

❖ **Tablets, capsules, sachets and dry powder inhalers**:

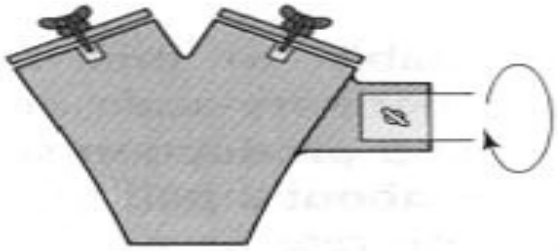
mixtures of solid particles (powder mixing)

❖ **Linctuses** - mixtures of miscible liquids

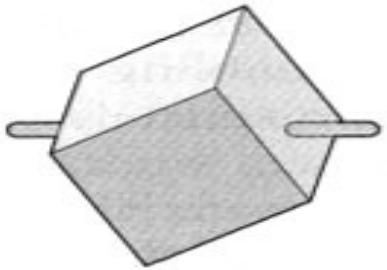
❖ **Emulsions and creams** - mixtures of immiscible liquids

❖ **Pastes and suspensions** - dispersions of solid particles

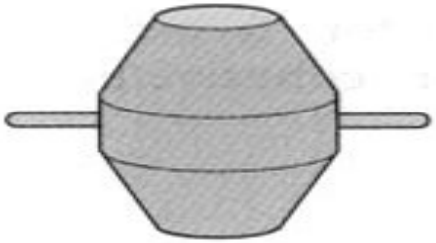
Different designs of the tumbling mixers



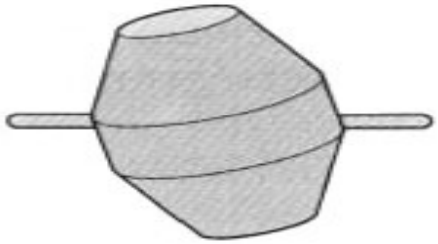
Y-cone mixer



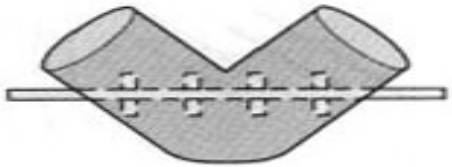
Rotating cube



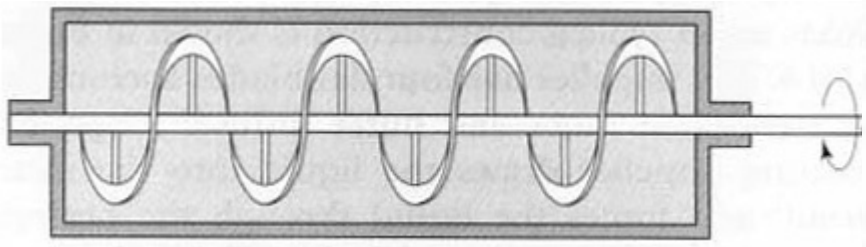
Double cone



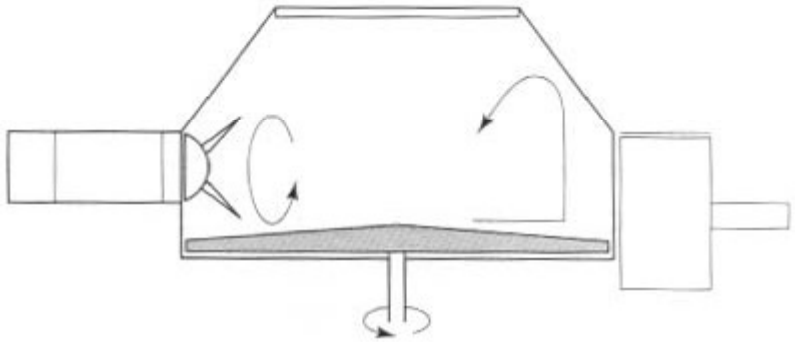
Oblique cone



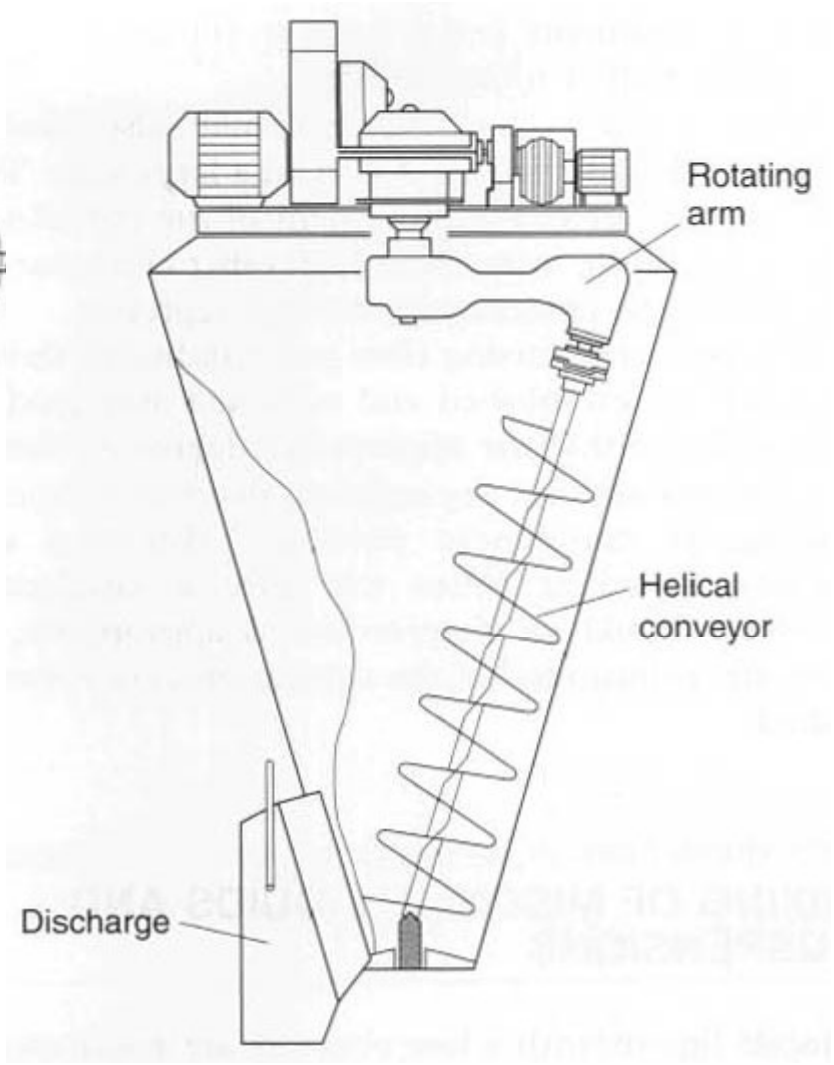
Twin shell (V) mixer
with agitator bar



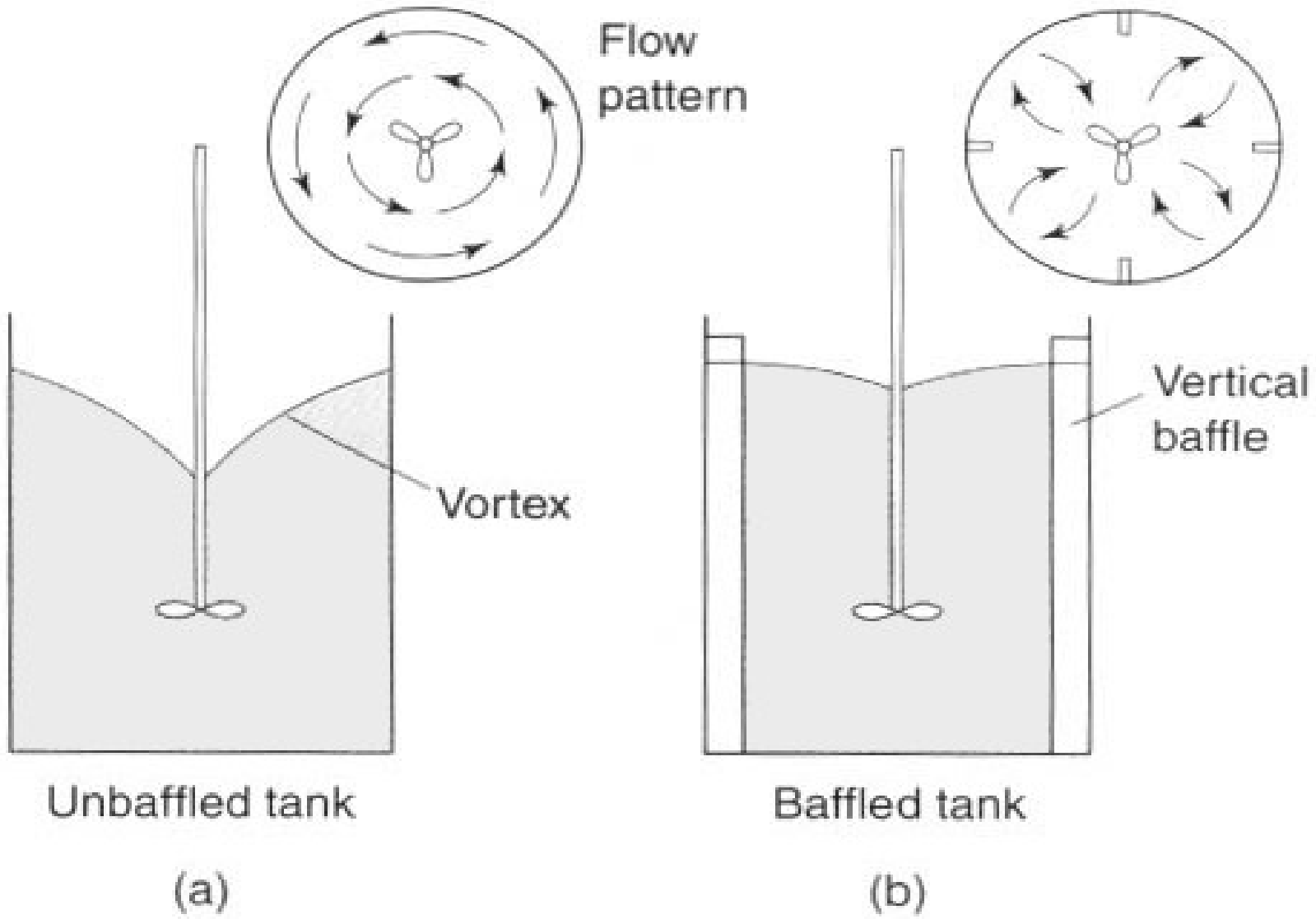
Ribbon agitator powder mixer



High-speed mixer-granulator



Nauta agitator powder mixer


Flow
pattern
Vortex
Unbaffled tank
(a)
Vertical
baffle
Baffled tank
(b)

Powder flow

- Pharmaceutical powders are largely used to produce tablets and capsules
- Powders with **good flow** and **compressibility** properties enables production of tablets & capsule with uniform weights and drug contents.

Derived properties of powders

1. Porosity

- Suppose a nonporous powder, is placed in a graduated cylinder such that the total volume occupied is called bulk volume, $\mathbf{V_b}$.

  $\mathbf{V_b = V_p + V}$ where Vp is the true volume of particles & V is volume of spaces between particles

- The volume of the spaces called the **void volume, V.**

$$\mathbf{V = [V_b - V_p]}$$

The porosity '**ε**' of powder is determined as the ratio of void volume to bulk volume.

$$\varepsilon = [V_b - V_p]/V_b$$

$$\text{Percent Porosity} = 100\varepsilon = [[V_b - V_p]/V_b]100$$

Example

- A sample of calcium oxide powder with a true density of 3.203 and weighing 131.3g was found to have a bulk volume of 82 cm^3 when placed in a 100-ml graduated cylinder. Calculate the porosity.

Solution

Volume of particle is 131.3 g / (3.203 g/cm^3) = 41cm^3

$\varepsilon = [V_b - V_p]/ V_b = [82 - 41]/ 82 = 0.5$

$= \underline{50\%}$

Densities of particles

- Density is defined as weight per unit volume (W/V).

Types of densities:

True density [Absolute density]**:** excludes the volume of the pores and voids within the sample

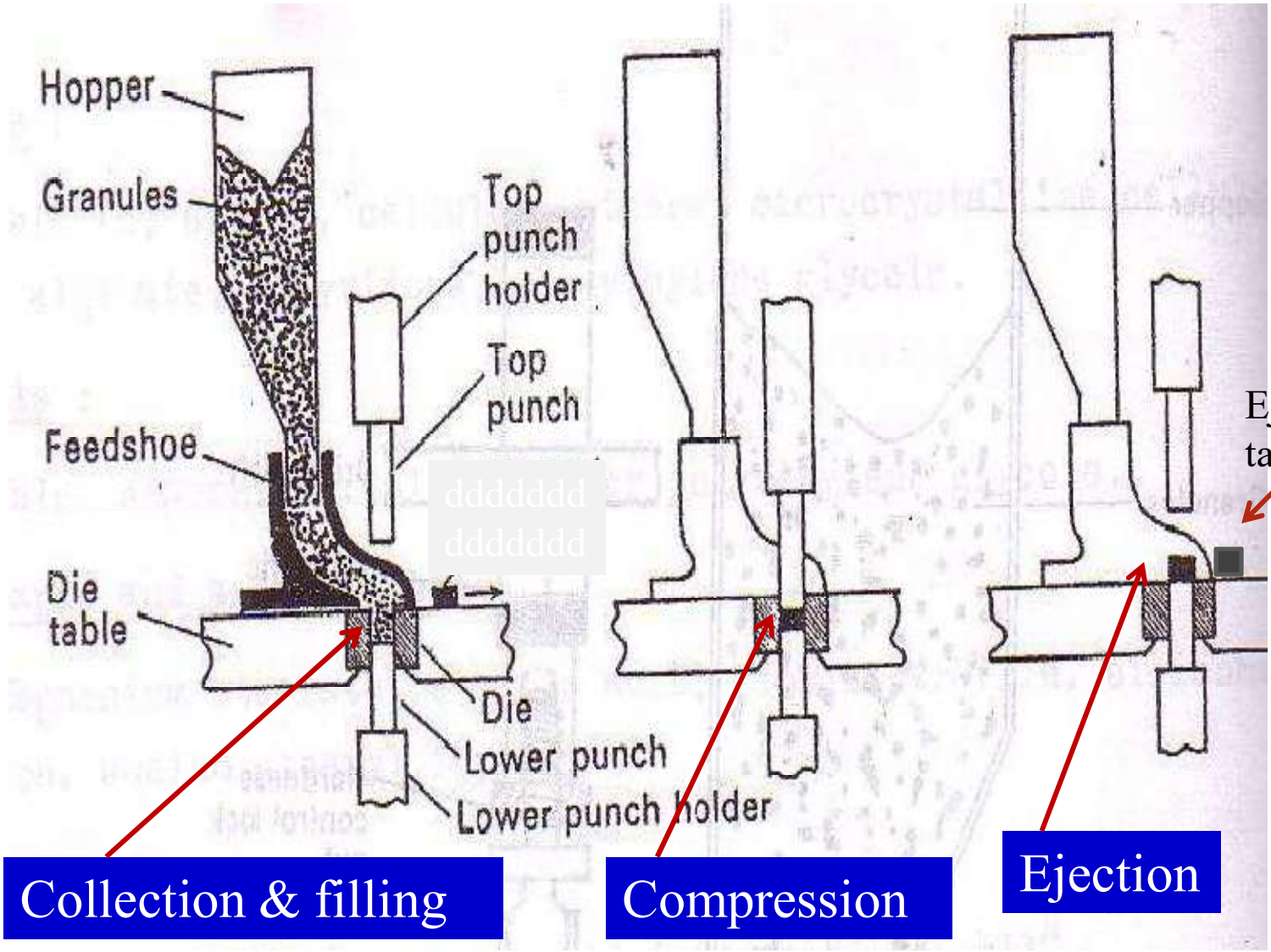
Bulk density (w/v) includes the volume of all of the pores within the sample.

Bulkiness = Specific bulk volume = reciprocal of bulk density

- It is an important consideration in powders packaging
- The bulk density of calcium carbonate vary from 0.1 to 1.3, and the lightest (bulkiest) type require a container about 13 times larger than that needed for the heaviest variety
- Bulkiness increases with a decrease in particle size.
- In mixture of materials of different sizes, the smaller particles sift between the larger ones and tend to reduce bulkiness

Flow properties

- Powders may be free-flowing or cohesive ("sticky").
- Effects of uneven powder flow can be:
  - Weight variation
  - Content nonuniformity
  - Capping or lamination (Excess entrapped air within powders)
  - Increase particle's friction with die wall causing lubrication problems
  - Increase dust contamination risks during powder transfer


Hopper
Granules
Top punch holder
Top punch
Feedshoe
Die table
Die
Lower punch
Lower punch holder
Ejected tablet
Collection & filling
Compression
Ejection

Qualitative tests to evaluate flowability of a powder

A. Carr's compressibility index

- A volume of powder is filled into a graduated glass cylinder and repeatedly tapped for a known duration. The volume of powder after tapping is measured.
- Carr's index (%) = [Tapped density – bulk density] 100/Tapped density

where

- Bulk density = weight / bulk volume
- Tapped density = weight / true volume or
  = weight / Tapped volume

Relationship between powder flowability and % compressibility [according to Carr]

Flow description	% Compressibility
Excellent flow	5 – 15
Good	16-18
Fair	19 – 21
Poor	22-35
Very poor	36-40

B. **Hausner ratio**

Hausner ratio = Tapped density/ Poured or bulk density

- Hausner ratio was related to interparticle friction:

**Value less than 1.25 indicates good flow (= 20% Carr)

Example: Powder with low interparticle friction, such as coarse spheres.

**Value greater than 1.5 indicates poor flow (= 33% Carr)

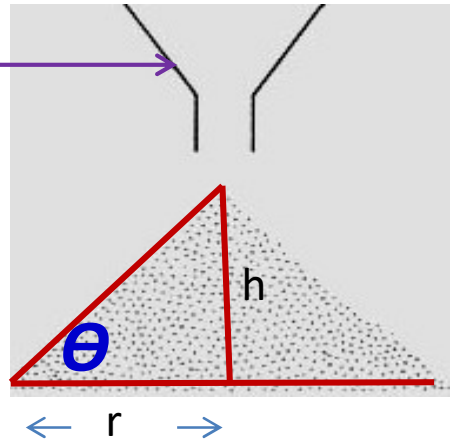
Example: More cohesive, less free-flowing powders such as flakes.

**Between 1.25 and 1.5, added glidant normally improves flow.

** > 1.5 added glidant doesn't improve flowm

Example Compete Carr's index & HR if Tapped & bulk densities are 9 & 8 g/ cm^3, respectively & the comment on powder flow

C. Angle of repose (Θ)



It is defined as the angle of the free surface of a pile of powder to the horizontal plane.

If a powder is allowed to flow onto a flat surface, a pile or heap of powder is formed. More cohesive & less spreadable materials form higher heap while materials that spread out and non-cohesive form low heap

Frictional forces in a loose powder can be measured by the angle of repose, θ.

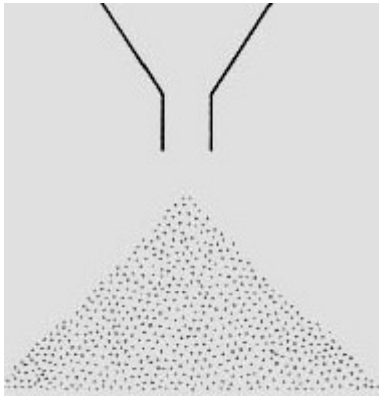
θ = maximum angle possible b/n surface of a pile of powder & horizontal plane

$$\tan \theta = h / r \text{ , where } r = d / 2$$

Procedure

- The sample is poured onto a horizontal surface and the angle of the resulting pyramid is measured.

Angle of repose	
Less than 20	Excellent flow
20-25	Very good flow
26-30	Good flow
30-34	Pass flow
Greater than 40	Poor flow



Note

The rougher & more irregular the particles' surface ,the higher will be the angle of repose

Factors affecting flow properties of powders

1. **Particle size & Distribution**

- Coarse particles are less cohesive than fine particles
- Particle sizes distribution having optimal proportion of fine & coarse particles improve flowability

2. **Particle Shape**

- Generally, spherical particles have better flow properties than irregular particles

3. **Particle's texture**

Particles with very rough surfaces are more cohesive and have a greater tendency to interlock than smooth surfaced particles

4. Surface Forces

- Reduction of electrostatic charges can improve powder flowability.
- Electrostatic charges can be reduced by altering process conditions to reduce frictional contacts

5. Moisture content of particle greatly affects powder's flowability

- Drying reduces cohesiveness & improve powder flow

6. Formulation additives (Flow activators)

- Flow activators such as **glidants** improve flowability of powders by reducing adhesion and cohesion

e.g. Talc, maize starch and magnesium stearate

Drying

- Removal of liquid from solid or semisolid or liquid preparation

How?

  - by thermal evaporation via latent heat of vaporization or
  - By using desiccants such as anhydrous CaCl2, activated silica gel, phosphorous pentoxide
  - By freeze drying via latent heat of sublimation
- Accomplished via heat transfer mechanisms
- Drying is a relative term, depending on type & nature of material to be dried
- It involves reduction of initial moisture content to acceptable final moisture content, the later value depends on material being dried

Objectives of drying

- To prepare dried powder extracts from plant or animal
- To prepare pharmaceutical granules
- To reduce bulk & weight of materials
- To preserve & stabilize animal & vegetable drugs by minimizing microbial growth
- To facilitate comminution of pharmaceutical materials
- To reduce chemical reactivity of water
- To enhance flowability & compressibility of powders
- To enhance stability of solid pharmaceutical dosage forms

Factors affecting drying

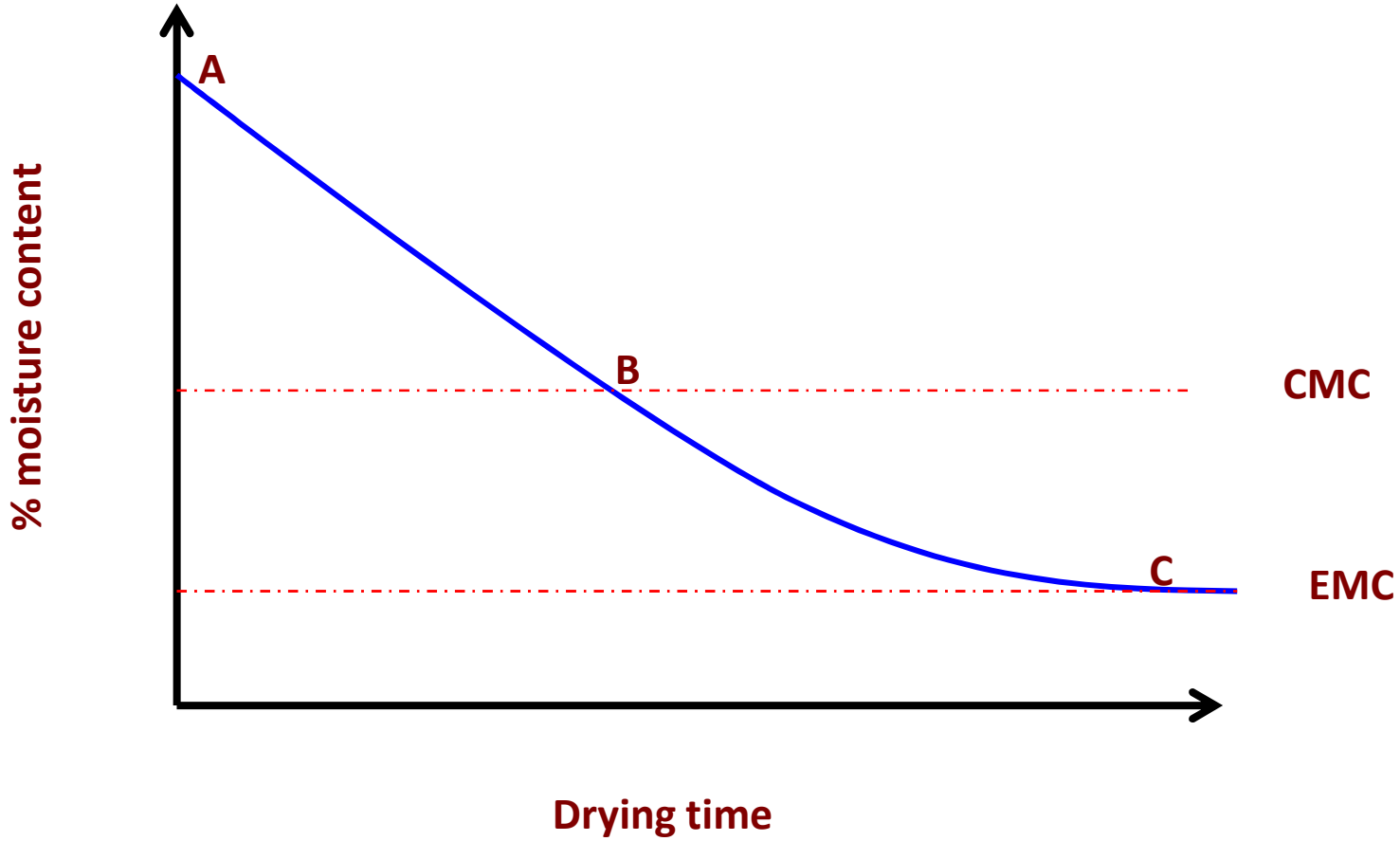
- Initial moisture content of materials to be dried
- Relative humidity of ambient air
- Surface area of materials to be dried
- Size & drying efficiency of drying equipment
- Drying temperature & time
- Nature of materials[porous, compact, etc]

Principles of drying

Drying rate shows different drying periods

1. Constant rate period
2. Critical moisture content
3. Falling rate period
4. Equilibrium moisture content

Drying curve



Constant rate [steady state] period…. [A to B]

- Discloses linear relationship b/n rate of evaporation & rate of replacement of moisture from below
- Rate of vaporization of moisture film from surface & rate of replacement of moisture from inner (below) surface are equal
- Rate of drying is governed by rate of heat transfer to the evaporating surface
- Rate of mass transfer balances the rate of heat transfer
- the temperature of the saturated surface remain constant

Falling rate period [FRP] ……[B to C]

- Begins when the rate of heat & mass transfer are no longer balanced
- Drying rate decline continuously since transfer of liquid from below the surface is inadequate to parallel vaporization rate

Internal mass transfer mechanisms that control FRP

- Capillarity in porous material
- Liquid diffusion & surface tension in continuous material
- Pressure-induced flow of liquid & vapour when material is heated from one side & vapour is removed from other side

Critical moisture content [CMC]… point B

- Moisture content at the end of constant drying period
- It is a function of nature of material [such as porosity], constant drying rate and particle sizes
- Drying spots begin to appear
- Drying steadily declines
- Surface water no longer replaced at a rate fast enough to maintain a continuous film

Note

- CMC has little use for standardization of drying operation
- Large particles have large CMC but small surface area to mass ratio & visversa
- Smaller particles rapidly attain CMC since internal moisture travel relatively shorter distance to reach its surface
- Case hardening [over-dried surface] leads to formation of a dry ,nonporous layer that act as a barrier to moisture diffusion since diffusivity decreases with moisture content

Equilibrium moisture content [EMC]… point C

- Drying rate is equal to zero
- Dried solid is at equilibrium with its surrounding
- Temperature & moisture content of solids remain constant

Drying methods

Broad classification

1. Drying by vaporization
   - Involves liquid –to- vapour transition
2. Sublimation
   - Involves liquid -to- solid-to vapour transition
3. Desiccation
   - Removes vapor by chemical agents called desiccants

Criteria for selection of drying methods

- Heat sensitivity of materials being dried
- Physical characteristic of the material
- Necessity for asepsis
- Nature of liquid to be removed
- Scale of operation
- Available sources of heat

Criteria for efficient drying

- Large surface area for heat transfer
- Efficient heat transfer per unit area
- Efficient mass transfer of evaporated water
- Efficient vapour removal

Equipment for drying

Classified based on heat transfer method

A. Wet solid pharmaceutical drier

1. Convective dryer
2. Conductive dryer

B. Dilute liquid pharmaceutical dryer

1. Drum dryer
2. Spray dryer
3. Freeze dryer

Convective dryer of wet solids

A. Fixed or static bed convective drying : Drying is from entire bed not from individual particles .Example:

1. Tray dryer or Truck dryer

- Equipped with heater, fan & air inlet & outlet devices
- Latent heat of vaporization is transferred convectively from the air

2. Tunnel dryer

- Modification of truck dryer since trucks are progressively moving by a moving chain via a tunnel
- Trucks are loaded on one side and then discharged at the other side of the tunnel after residing in the heating chamber for reasonable time

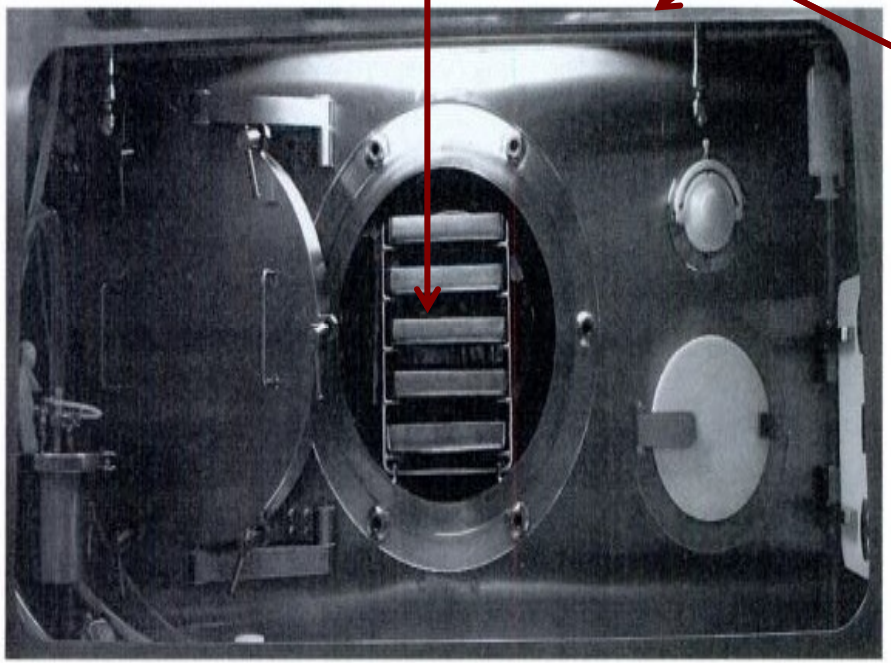
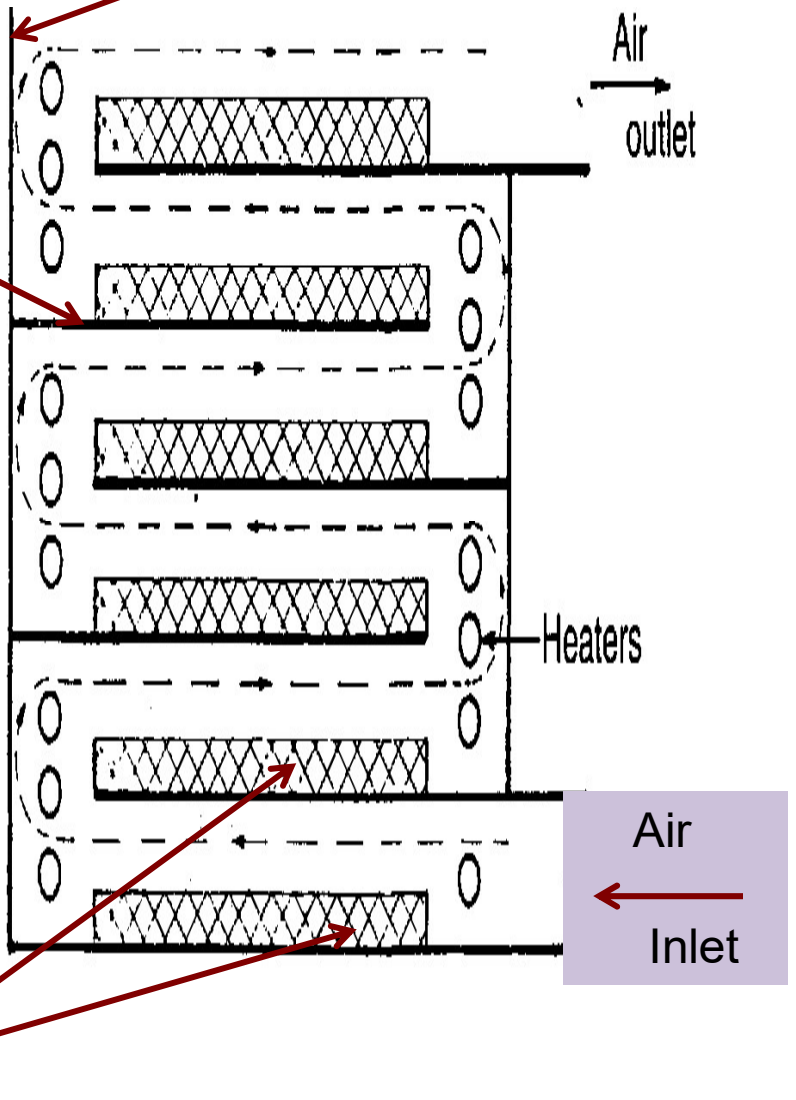


FIGURE 3 Tray drying isolator. *Source*: Courtesy Powder Systems Ltd., Liverpool, UK.



B. Dynamic convective dryer: Drying is from individual particles not from entire bed

Example: Fluidized bed dryer [FBD], Rotary dryer

- Heated & filtered gas is allowed to flow upward via a bed of particulate solids at a velocity higher than falling velocity of particles
- Thus particles remain suspended in the gas stream for sometimes
- Solid particles are said to be fluidized since the mixture of solids & gas behave like a liquid

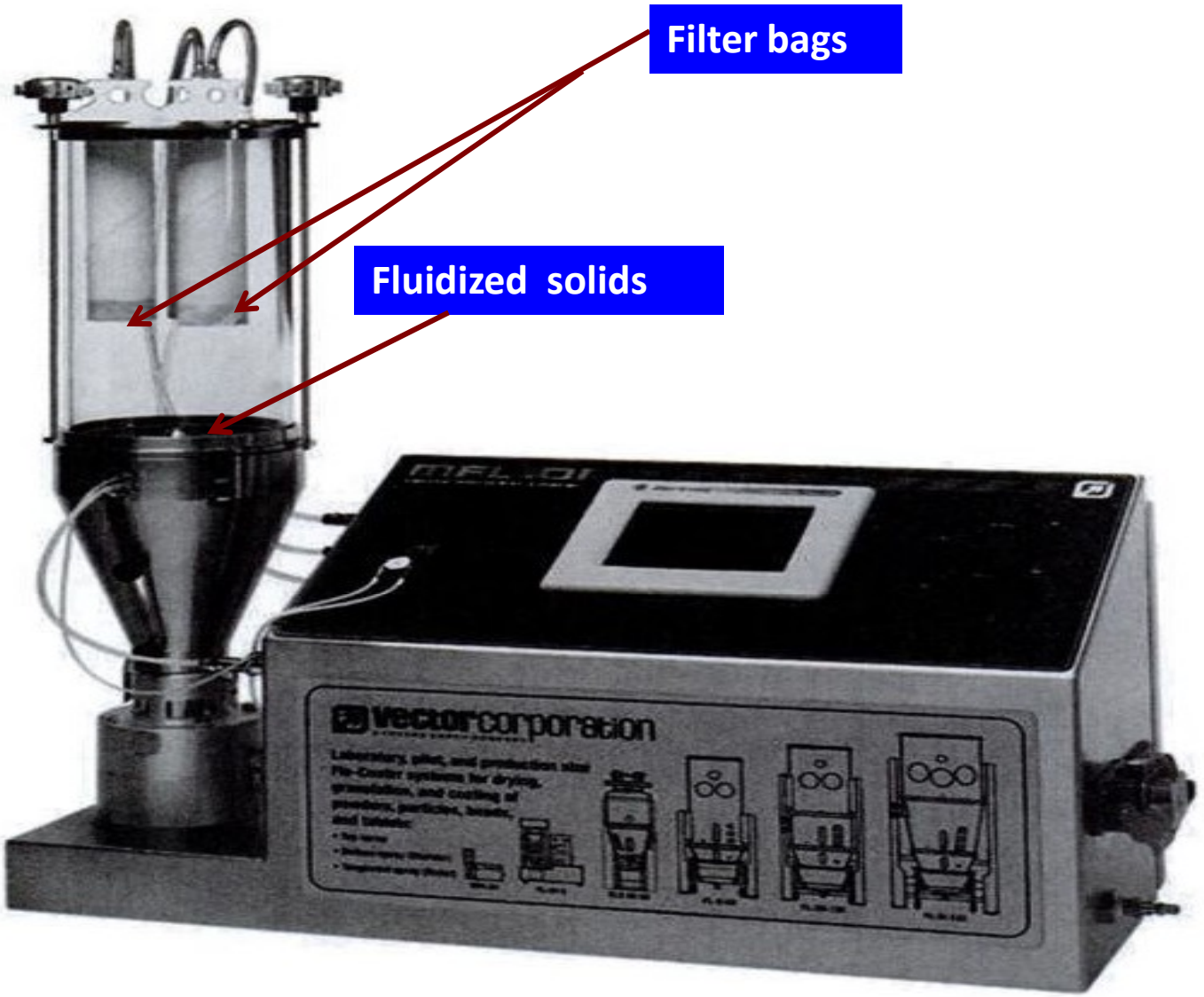
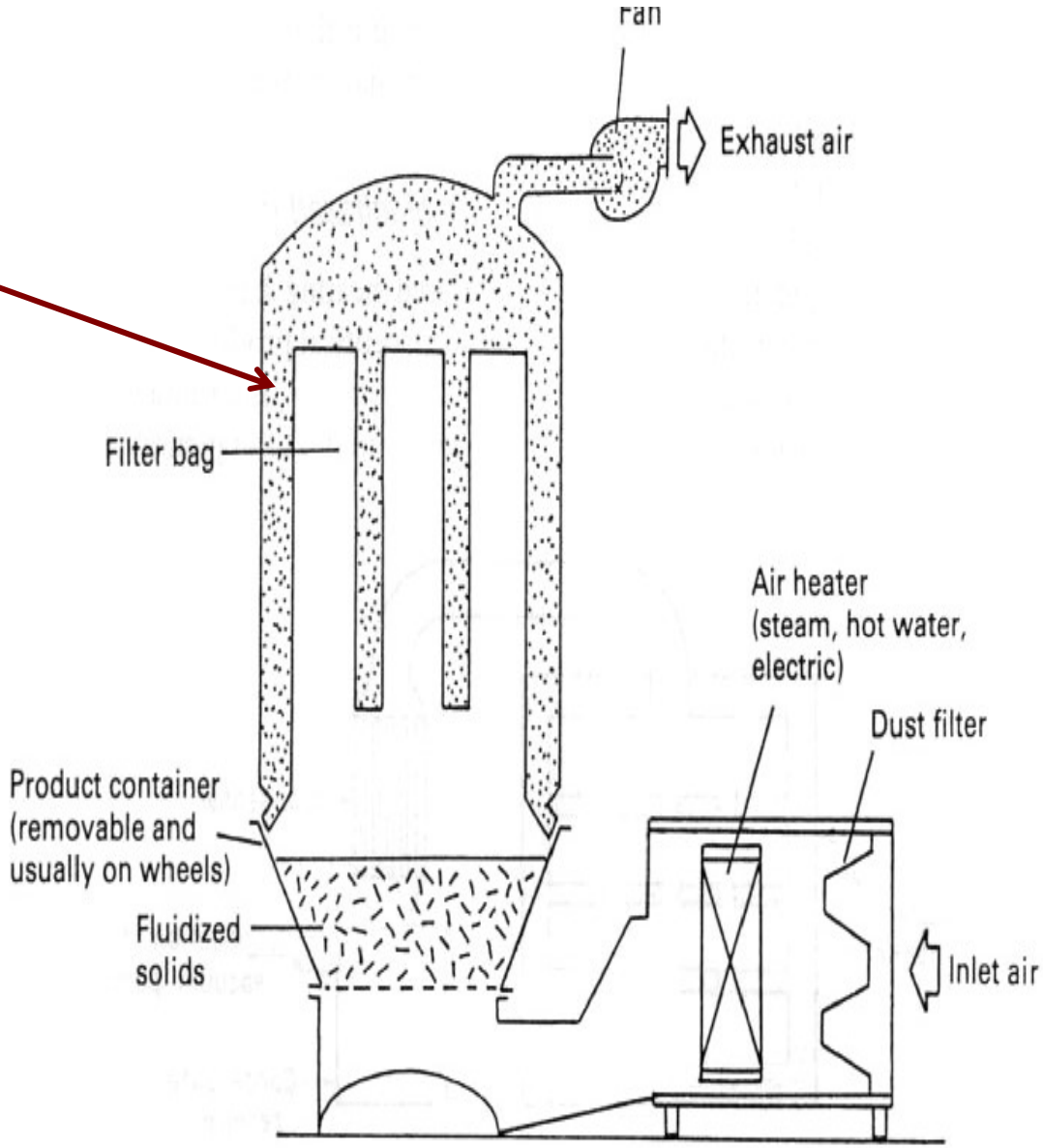


FIGURE **Fluidized Bed Dryer**

Fluidized Bed Dryer



FBD is equipped with:

- ❖ Fluidized solid containers
- ❖ Filter bags
- ❖ Heaters
- ❖ Fan
- ❖ Air inlet & out let gate
- ❖ Recirculation control

Advantages of FBD

- High drying rate[20-30 minutes] due to efficient heat & mass transfer
- Drying is from individual particles not from entire bed
- Provides uniform & precisely controlled drying temperature
- Produce free flowing products owing to fluidization state of the system
- High out put due to short drying time

Disadvantage of FBD

- ❖ Production of fine particles

Reason: High fluidization turbulence causes attrition of materials

- ❖ Generation of electrostatic charges

Reason :Vigorous movements of particles in hot air

Conductive drying of wet solids

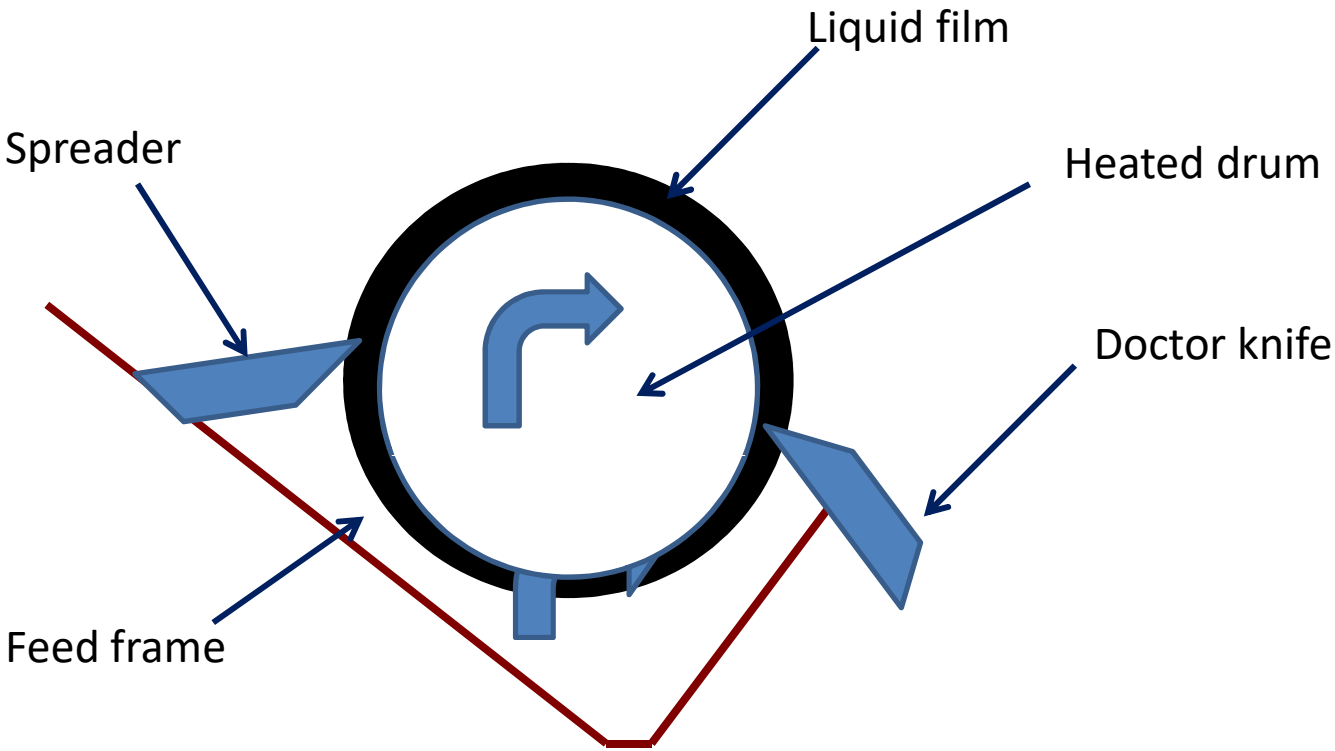
Opened Vacuum Oven

- Wet solid is in thermal contact with hot surface
- Heat transfer occurs by conduction
- Equipped with steam pressure in jacketed vessel
- Locked with airtight seal
- Connected to vacuum pump via condenser & condensate receiver

A. Dilute liquid pharmaceutical dryer

Drum dryer [Film dryer]

- Heated internally & rotated on its longitudinal axis
- The drum dips into feed pan, thus liquid preparation is applied to surface of drum & spread to form film
- Drying rate is controlled by manipulating speed of rotation of the drum & its temperature
- Dried product is scrapped from drum by doctor knife
- Critical operation conditions include feed rate, film thickness, speed of drum rotation & drum temperature



Drum dryer

Advantage of drum dryer

- Rapid drying since thin film facilitate rapid heat & mass transfer
- Economic utilization of space since it is compact
- Short heating time, few seconds
- Drying temperature can be reduced by enclosing the drum within vacuum jacket

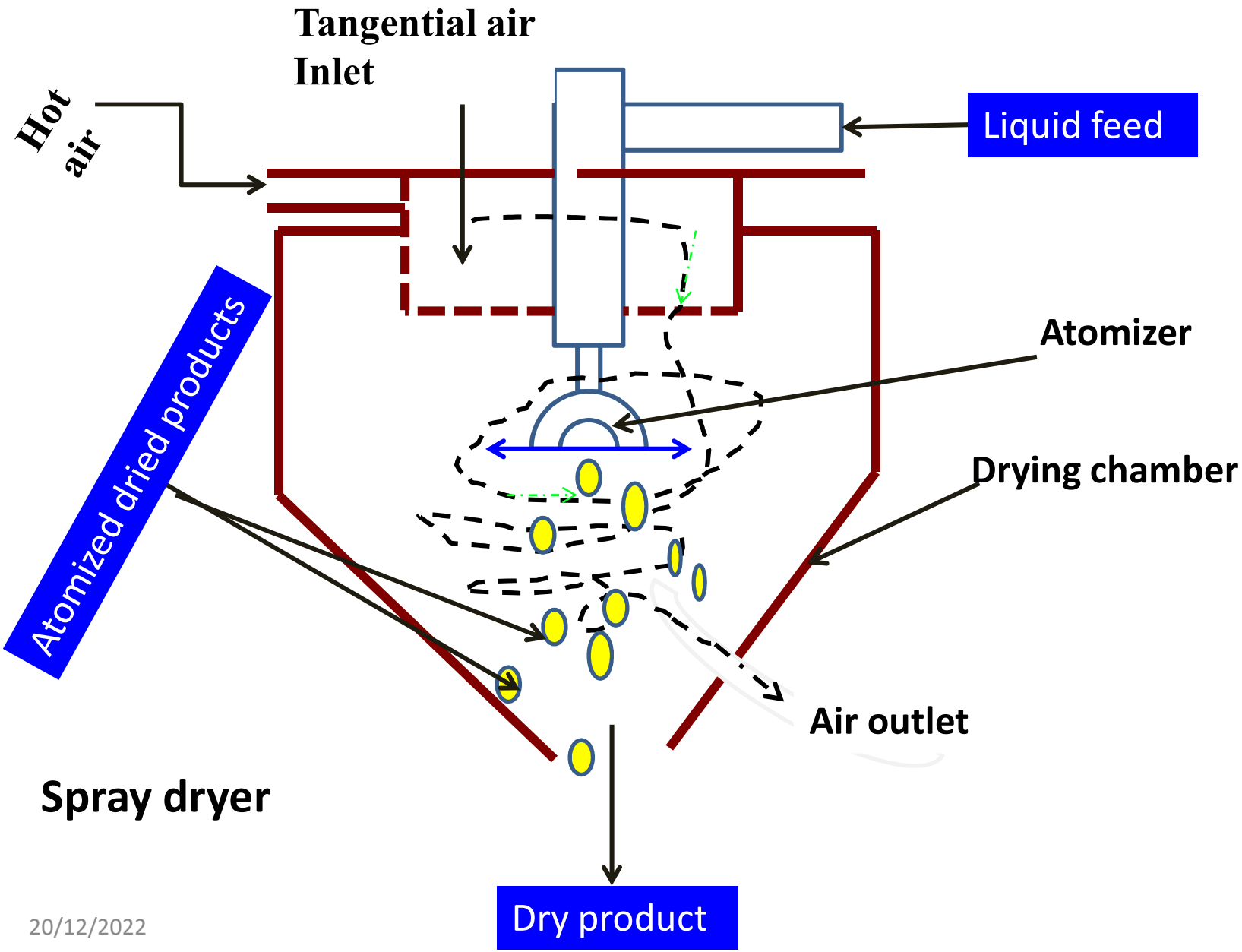
Disadvantage

Operation conditions are critical

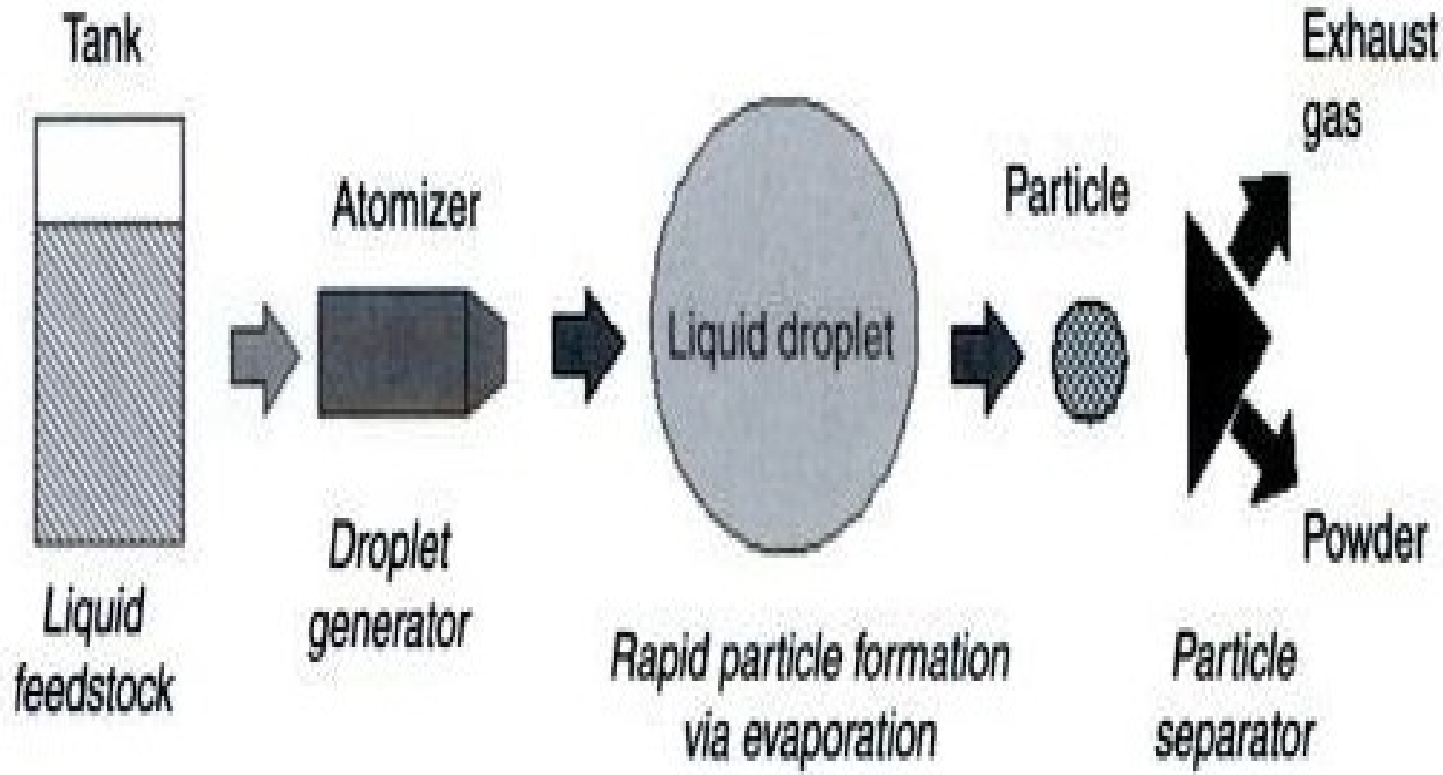
Spray dryer

- Provides large surface area for heat & mass transfer
- Atomize liquid preparation to small droplet
- Atomized droplets are sprayed into stream of hot air& dried as individual solid particles

Examples: Jet atomizer , Rotary atomizer


Tangential air
Inlet
Hot
air
Liquid feed
Atomizer
Drying chamber
Atomized dried products
Air outlet
Spray dryer
Dry product

Schematic presentation of spray drying process

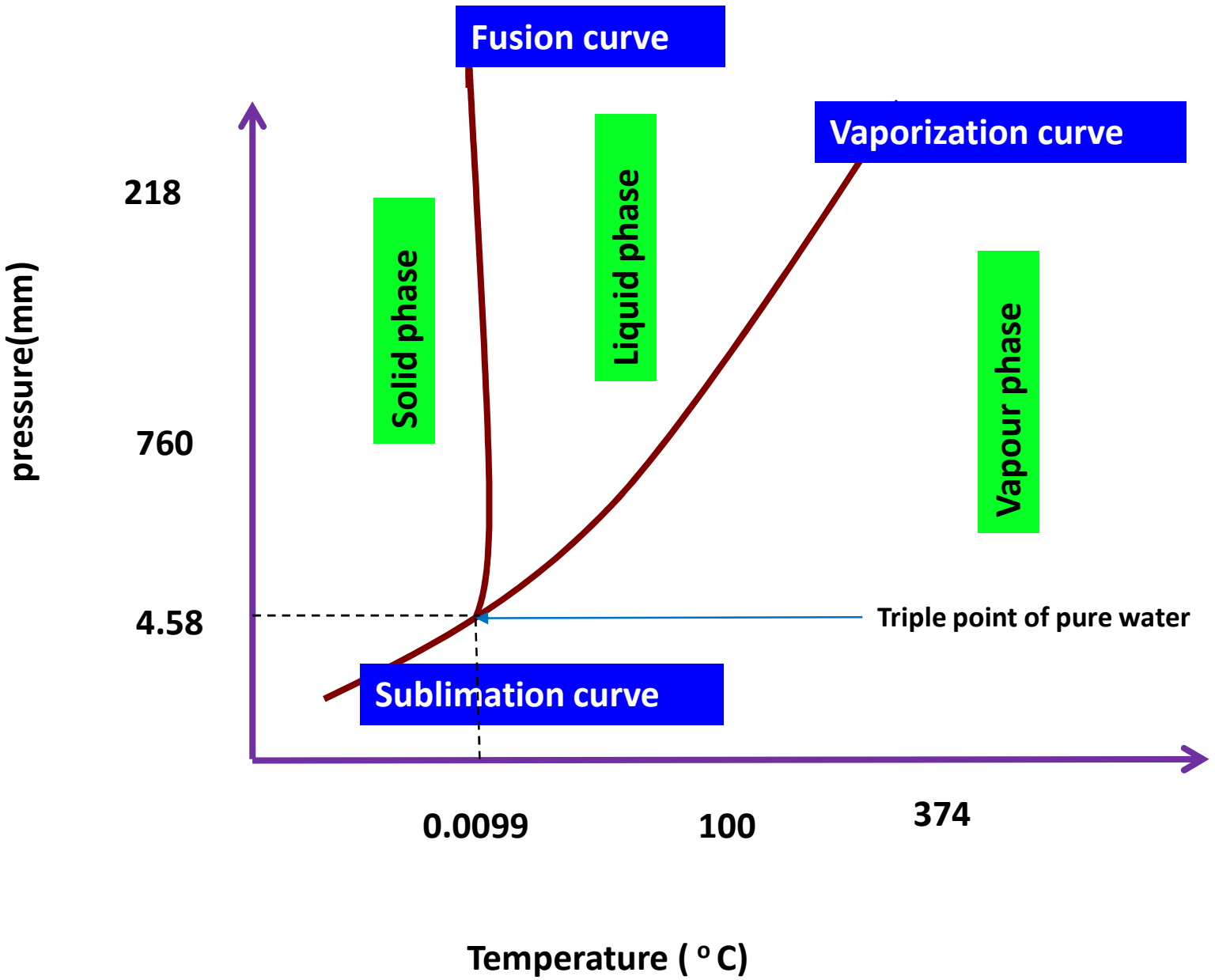


Advantages of spray dryer

- Dry liquid droplets within fraction of seconds
- Drying occurs at low temperature since latent heat of vaporization is used & temperature of particles is kept low by evaporative cooling
- Products have:
  - ✓ high bulk density[due to inner void space] & rapid dissolution[due to large surface area] of spherical articles
  - ✓uniform & controllable particle size
  - ✓Excellent flow & compaction properties[spherical in shape]

Disadvantage of spray dryer

- ❖ Bulky & expensive
- ❖ Low overall thermal efficiency
- ❖ **Reasons**
  - Exhaust air is still hot
  - Some inlet air leaves dryer without making contact with particles


Fusion curve
Vaporization curve
Solid phase
Liquid phase
Vapour phase
218
760
4.58
pressure(mm)
Triple point of pure water
Sublimation curve
0.0099
100
374
Temperature (° C)

Freeze dryer/Lyophilizer/

- Lyophilization or freeze-drying is a process in which water is removed from a product after it is frozen and placed under a vacuum, allowing the ice to change directly from solid to vapour without passing through the liquid phase.

- Freeze drying or "lyophilization," is a drying process employed to convert solutions of labile materials [sensitive to heat, moisture or oxygen] into solids of sufficient stability for distribution & storage

Example

Blood serum, Plasma, Moisture sensitive antibiotics , enzyme preparations & microbial cultures

- Used to dry pharmaceutical preparations for reconstitution[re-dissolved or resuspended]

Components of Freeze dryer

1. Vacuum drying chamber [containing temperature controlled shelves, connected to a ‘‘condenser’’ chamber via a large valve]
2. Vacuum source(pump)
3. Heat source(by conduction &/or radiation)
4. Vapour removal system (pump, desiccant or condenser)

Freeze-drying process

- Lyophilization process consists of three separate, unique, and interdependent processes:
  1. Freezing
  2. Primary drying (sublimation)
  3. Secondary drying (desorption)

1. Freezing

- Freezing of liquid pharmaceuticals takes place below triple point of water called eutectic point
- Initial liquid preparation is frozen in the temperature range -10 to -40 ^{o}C & pressure 10-30 N/m^{2}
- Thus, most of the water from the system is changed to ice and all solutes into solids, either crystalline solids or a glass
- The ice is removed from frozen preparation by sublimation

2. Primary drying stage

- ❖ Reduces moisture content of frozen preparation to 0.5% of its initial moisture
- ❖ Latent heat of sublimation is used
- ❖ Vapour is continuously removed

3. Secondary drying stage

- Applied at the end of primary drying stage
- Temperature of the system is raise to 50 to 60 ^{o} **C**
- Results in complete drying of solid materials

Advantages of lyophilization

- Enzyme action is precluded
- Chemical decomposition due to hydrolysis is minimized
- Produces readily reconstitutable porous products
- No concentration of solution prior to drying ,hence salts do not concentrate & no protein denaturing as occurs via other thermal methods
- Product oxidation is minimized since drying occurs under vacuum & no direct air-product contact

Disadvantages

- The plant is very expensive
- The drying process is very slow
- Cannot be a general drying method
- Produce very hygroscopic products

Reason

Products are porous, readily soluble & completely dried

Solution

Dry liquid preparation in their final containers & seal insitu, immediately after secondary drying stage

Unit 4: Granulation and Excipients

- Process where primary powder particles are made to adhere to form larger, multiparticle entities called granules
- Pharmaceutical granules can be used to prepare tablet & capsule [size:0.2 - 4 mm], serve as intermediate products[size: 0.2 to 0.5 mm] or used as a dosage form on its own[size > 4mm]
- Granulation commences after initial dry mixing of powdered ingredients with the aim of ensuring uniform distribution of each ingredient via the mix
- After granulation, granules either be packed to form dosage form or mixed with other excipients prior to tablet compaction or capsule filling

- Granulation is the process of collecting particles together by creating bonds between them. Bonds are formed by compression or by using a binding agent
- Tablet require inactive ingredients for additional bulk, improved flow, flavouring, better compressibility, improved disintegration or enhanced appearance
- Ingredients may be incompatible due to particle size, particle density, flow characteristics, compressibility, & moisture content resulting in segregation during blending , transfer of product to press &/or tablet press

Remedy: Dry mix active agent with diluent, then granulate the mix by gradual addition of granulating agent [water, starch mucilage, gelatine solution , sucrose solution or co-solvents] with continuous mixing

Reasons for granulation

- Prevent demixing of constituents
- Improve flow properties of the mix
- Improve compaction characteristics of mix
- Prevent caking of hygroscopic constituents
- Reduce dusting of toxic substances
- Increase compressibility
- Produce particle-size uniformity, thus content uniformity

Excipients

- Granulation requires mixing drug with excipients
- Excipients can be largely divided into two categories
  - ✓Bulking agents [diluents or fillers]
  - ✓Functional additives
    - Binders
    - Disintegrants
    - Lubricants
    - Colorants
    - Stabilizing agents
- Choice of excipients depends on process involved, nature of drug, formulator interest & cost of excipients

Examples	
Filler[bulk up a tablet]	**Disintegrates [help tablet break up]**
▪Lactose [very common]	1. Pregelatinized starch
▪Dicalcium phosphate	2. Microcrystalline cellulose*
▪Starch	3. Croscarmellose*
▪Pregelatinized starch	4. Crospovidone*
▪Microcrystalline cellulose	5. Sodium starch glycolate*
	6. Low-substituted hydroxypropylcellulose*
	* = Super-disintegrants

- Disintegrant is added to a formulation to overcome cohesive strength imparted during compression
- It can be either intra-granular, extra-granular, or both
- On contact with water, disintegrant can draw water into the tablet, swelling and forcing the tablet apart
- It facilitates break up of tablet in the body, hence increasing the surface area for dissolution
- **Super-disintegrants** are effective at much lower amounts compared to the native disintegrants

➢ Comprise three groups:

- ❖ Modified starches
- ❖ Modified cellulose
- ❖ Cross - linked povidone

Lubricants

- Prevent powders from sticking to metal components of the tablet press and tablet-press tooling
- Usually not added till prior to filling or tableting of the granules

Examples:

- ❖ Magnesium stearate [Most commonly used]
- ❖ Talc
- ❖ Calcium stearate
- ❖ Stearic acid
- ❖ Wax
- ❖ Hydrogenated vegetable oil

Binders used in granulation to help powders or particles fuse to one another

- Consist of a wide variety of sugars & polymers [Natural, semi-synthetic & synthetic]. **Examples**

Sugars used include sucrose, glucose & sorbitol.

Natural polymeric binders : Alginic acid, sodium alginate, acacia, gelatine and starch

Semisynthetic binders :Sodium carboxymethylcellulose hydroxypropylmethylcellulose,hydroxypropylcellulose , Ethylcellulose & methylcellulose

Synthetic binders : Polyvinylpyrrolidone & polyethylene glycol.

- Binder should impart adequate cohesion without retarding disintegration or dissolution.
- Binders can be added either as a solution, paste or dry powder
- Binders added as dry powders are mixed with other powders prior to agglomeration, dissolving in water or solvent added during granulation, or added prior to compaction.
- Solution binders can be sprayed, poured, or mixed with the powder blend for agglomeration and are generally more effective

Glidants [Flow enhancers or antiadherent]

- Improve flowability of powders & granules by virtue of their low adhesive potential, and ability to reduce inter-particle adhesion
- Reduce powder or granules picking by or sticking to punch faces adhesion between the powder and the punch faces and thus prevent particles ***picking or*** sticking to the punches

Examples: Colloidal silicone dioxide, talc

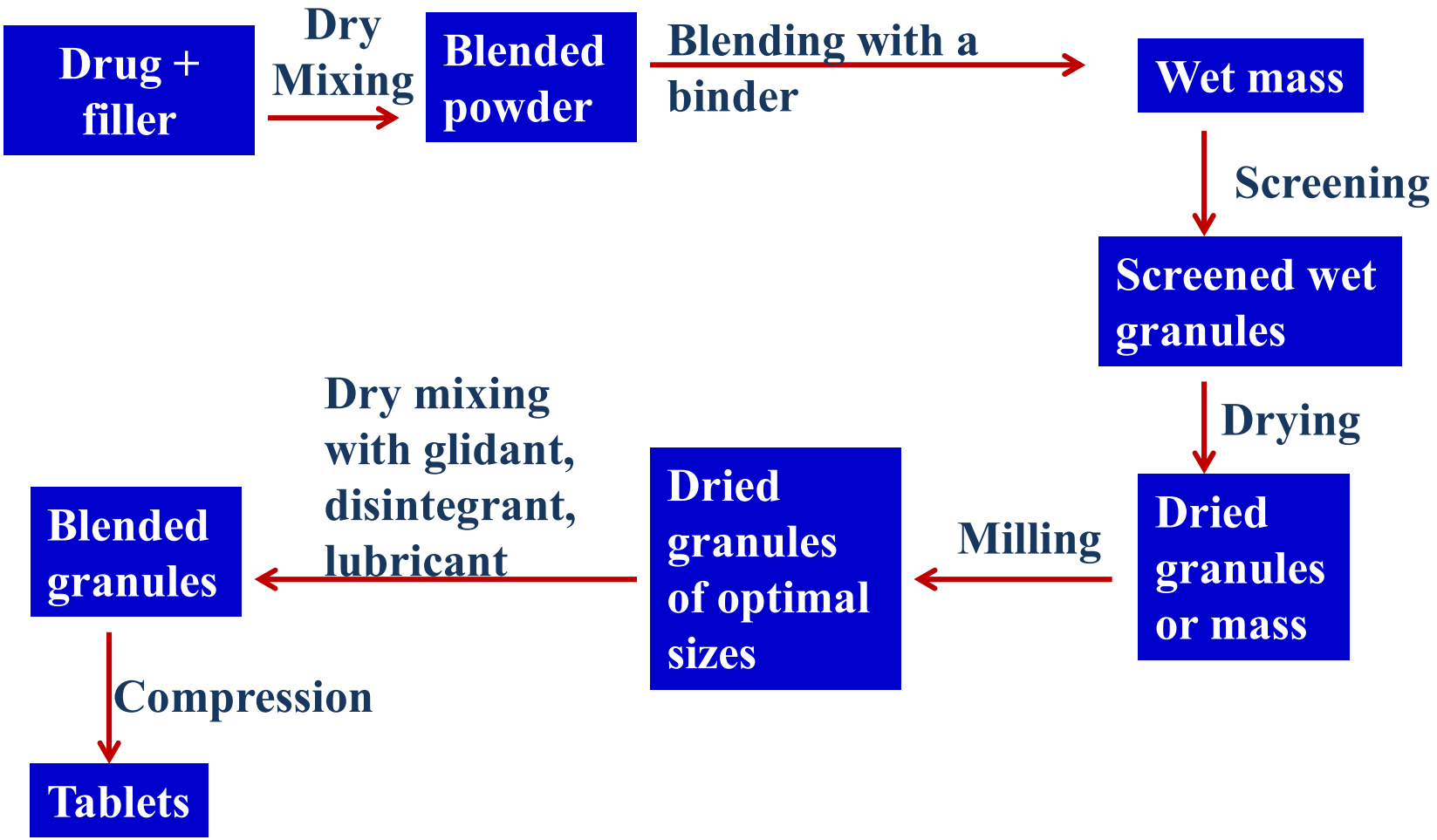
Other excipients

- Colorants: Iron oxides, titanium dioxide
- Sweetening agents: Saccharine , sugar
- Flavouring agents
  - Give more pleasant taste or mask unpleasant taste.
  - Added to granules as alcohol solution during mixing of granules since they are thermo-labile
- Coating aids
- Stabilizers : Preservative, antioxidant, buffering agent
- Release rate modifiers

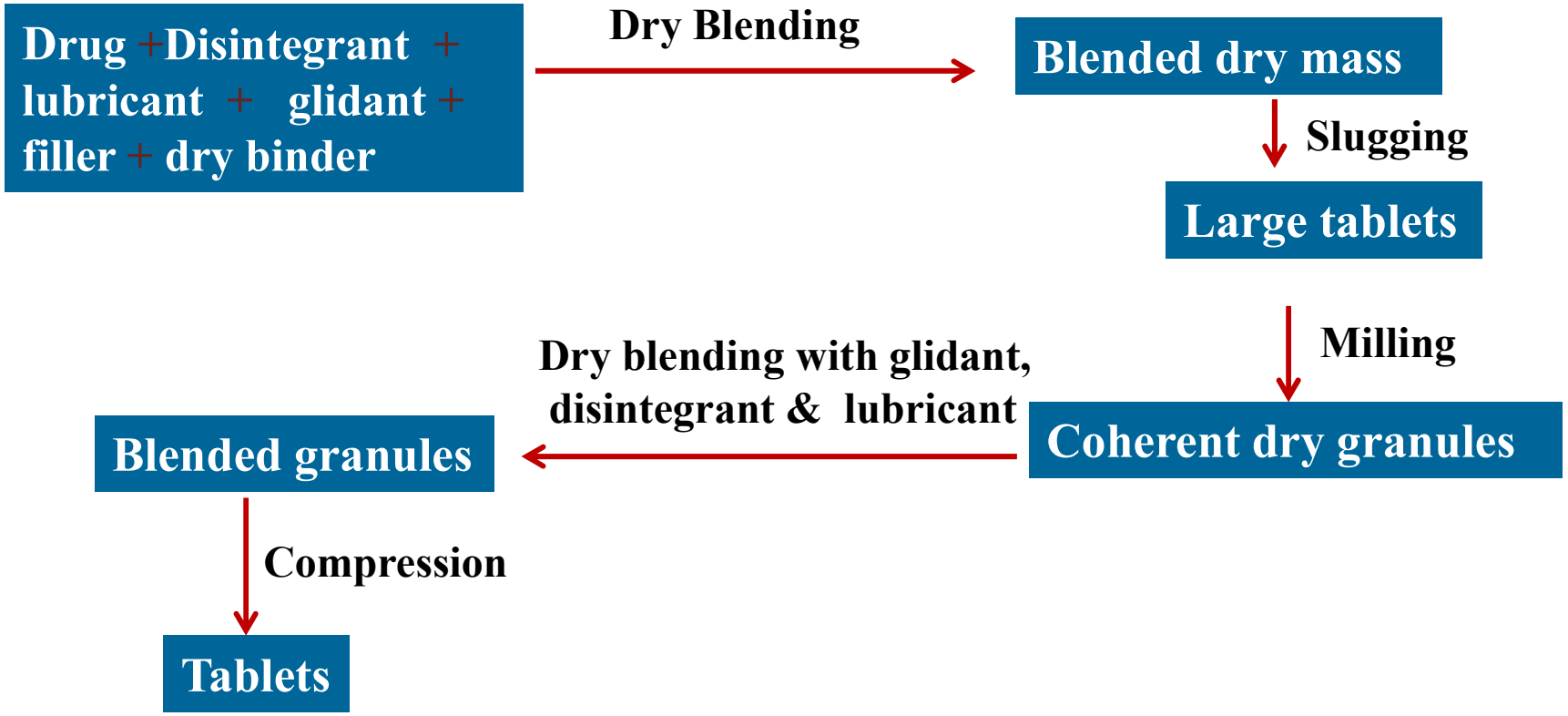
Three basic tablet manufacturing techniques :

1. Wet granulation
2. Dry granulation
3. Direct compression

Wet granulation is used for heat & moisture stable drug

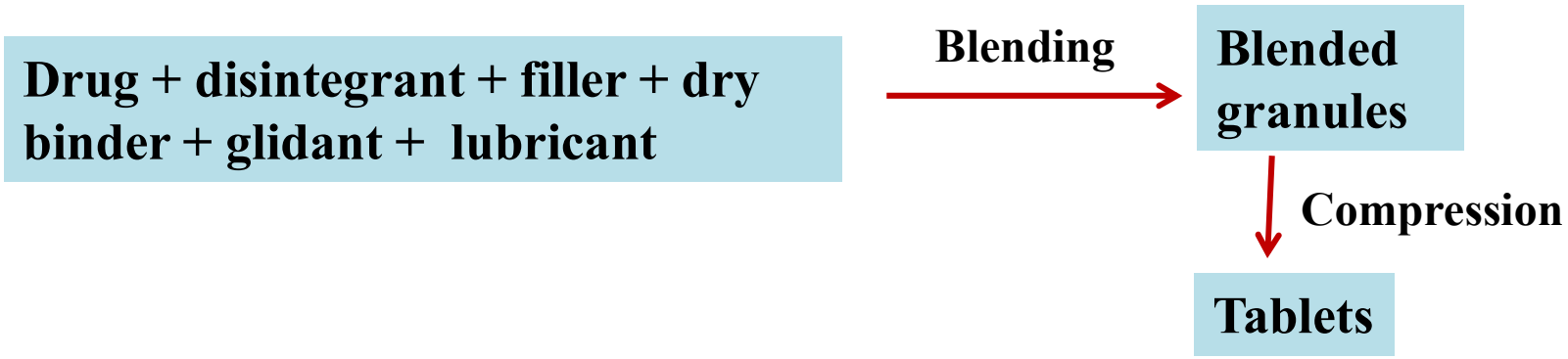


Dry granulation is used for formulation containing moisture &/or heat sensitive components



Direct compression is used for formulation having [**]

- ❖ good flow properties
- ❖ compressible components



- ❖ Direct compression is generally done for crystalline materials having good physical properties [**]
- ❖ Main advantages of direct compression are time saving, safety of operations and low cost

Mechanisms of granule formation

A. Dry method

- Particle adhesion takes place due to applied compression pressure using a:
  - tablet press
  - slugging tooling or
  - roller compactor known as a chilsonator
- A compact [slug]or sheet larger than granule size is produced
- Required granule size is attained by milling & sieving

B. Wet method : Formation of granules starts with particle-particle contact & enhanced by mechanical agitation & liquid binder bridging effect.

Granulation stages [3]

1. **Nucleation**: A № of particles join each other to form nuclei that serve for further granule growth
2. **Transition**: Characterized by presence of a large № of small granules with a fairly wide size distribution. Serve as a suitable end-point for granules used in capsule & tablet production since small granules produce uniform die fill volume than large granules do.
3. **Ball growth**: Subsequent agitation results in small granules coalescence hence formation of large ball sized granules. As ball growth commences large granules unsuitable for pharmaceutical purposes can be produced, thus needs control

Pharmaceutical granulation equipment

A. Fluidized-bed granulators

- Heated and filtered air is blown or sucked through bed of unmixed powders to fluidize the particles & mix the powders
- Fluidization is actually a very efficient mixing process

Table 25.1 Apparatus, process and product variables influencing fluidized-bed granulation

Apparatus parameters	Process parameters	Product parameters
Air distribution plate	Bed load	Type of binder
Shape of granulator body	Fluidizing air flow rate	Quantity of binder
Nozzle height	Fluidizing air temperature	Binder solvent
Positive or negative pressure operation	Fluidizing air humidity	Concentration of granulating solution
Scale-up	Atomization Nozzle type Spray angle Spraying regime Liquid flow rate Atomizing air flow rate Atomizing air pressure Droplet size	Temperature of granulation solution Starting Materials Fluidization Powder hydrophobicity

B. Dry granulators

- Dry granulation converts primary powder particles into granules using application of pressure without liquid granulating agent. No heat-temperature impact on products
- Dry granulation equipments include:

Sluggers or Roller compactors and **Miller**

- **Sluggers** are Conventional tablet press or, more usually, a large heavy duty rotary press that are used to form slug via a process called slugging[compressing dry powders into slug]
- **Roller compactors** : the powder mix being squeezed between two rollers to form a compressed sheet
- **Miller** for breaking up slugs or intermediate products into appropriate granule sizes

Unit 5:Tablets and compaction

4.1. Quality attributes

4.2. Manufacturing

4.3. Fundamentals of powder compaction

4.4. Excipients

4.5. Tablet types and testing(QC)

Introduction

- Tablets are solid preparations each containing a single dose of one or more active ingredients & obtained by compressing uniform volumes of particles
- Intended for oral administration. Some are swallowed whole, some after being chewed, some are dissolved or dispersed in water before being administered & some are retained in the mouth, where the active ingredient is 'liberated and absorbed. Thus, a variety of tablets exists and the type of excipients and the way in which they are incorporated in the tablet vary between the different types
- Tablets are administered for systemic or local effects

Advantages of tablets:

- Chemically, physically & microbiologically more stable than liquid dosage forms
- Have accurate dose
- Convenient to handle & self-administer
- Prepared in a versatile way with respect to their use & drug delivery
- Can be mass produced
- Elegant with consistent quality & low price
- Tamperproof

Disadvantages of tablets

- Poor bioavailability of hydrophobic drug from tablet
- Gastric irritation from tablet of irritant drug

5.1. Quality attributes of tablets

1. Must have correct dose of the drug
2. Must have consistent appearance, weight & size
3. Must release drug in a controlled & reproducible way
4. Must be biocompatible, i.e. never include excipients, contaminants and microorganisms harmful to patients
5. Must have sufficient mechanical strength to withstand fracture and erosion during transportation
6. Must be chemically, physically & microbiologically stable during its shelf-life
7. Must be packed in a safe manner

Tablets are produced using tablet press

Basic components of tablet presses:

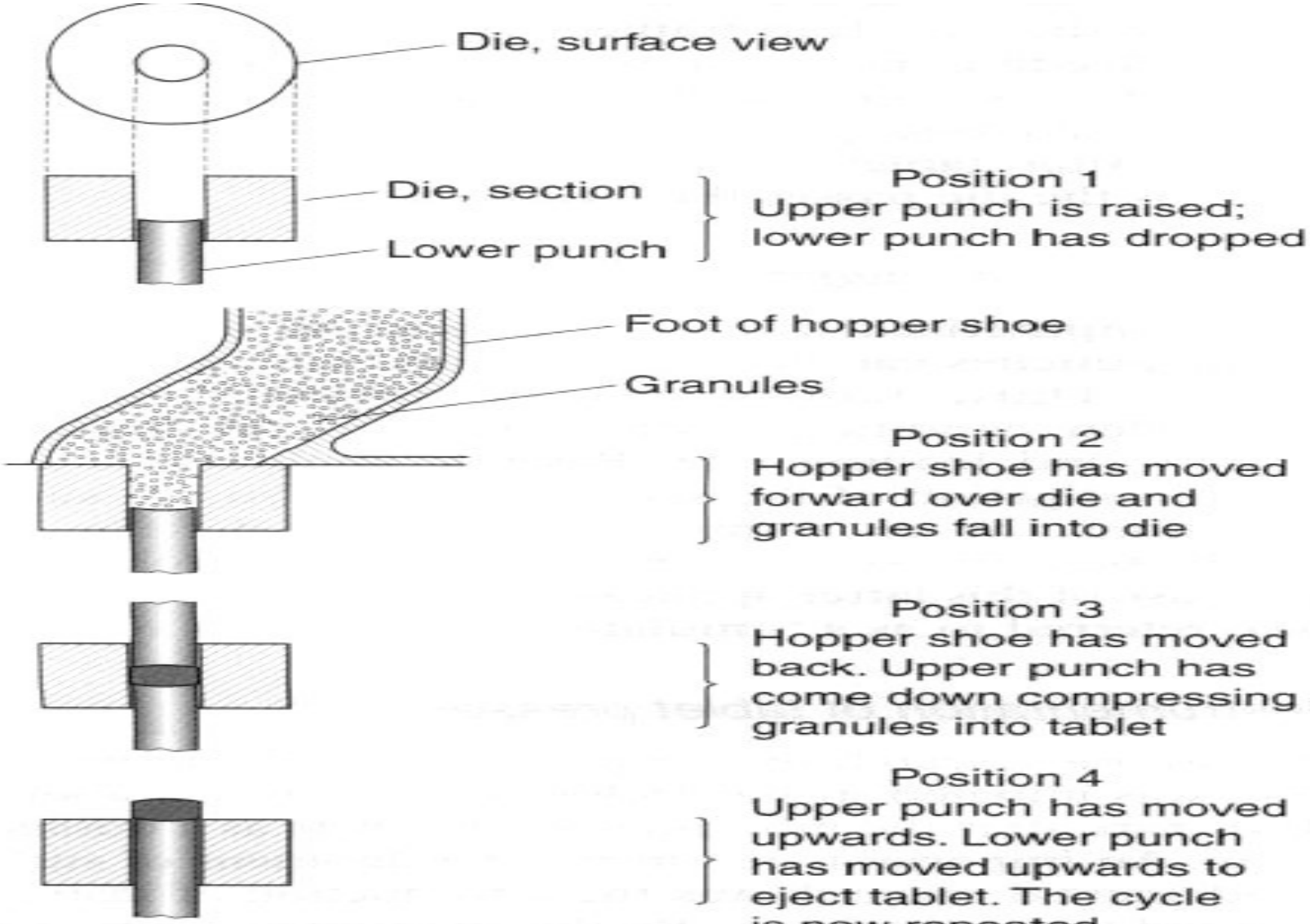
- Hopper for holding and feeding granules
- Dies that define the thickness, size[diameter] and shape of the tablet.
- Punches for compressing the granules within the dies
- Cam tracks for guiding movement &/or position of punches
- Feed frame controls filling of moving granules from hopper into the dies
- Tablet adjuster **:** Used to adjust volume of powder to be compressed and so determines weight of tablet
- Ejection adjuster **:** Facilities ejection of tablet from the die cavity after compression

5.2. Manufacturing of tablets

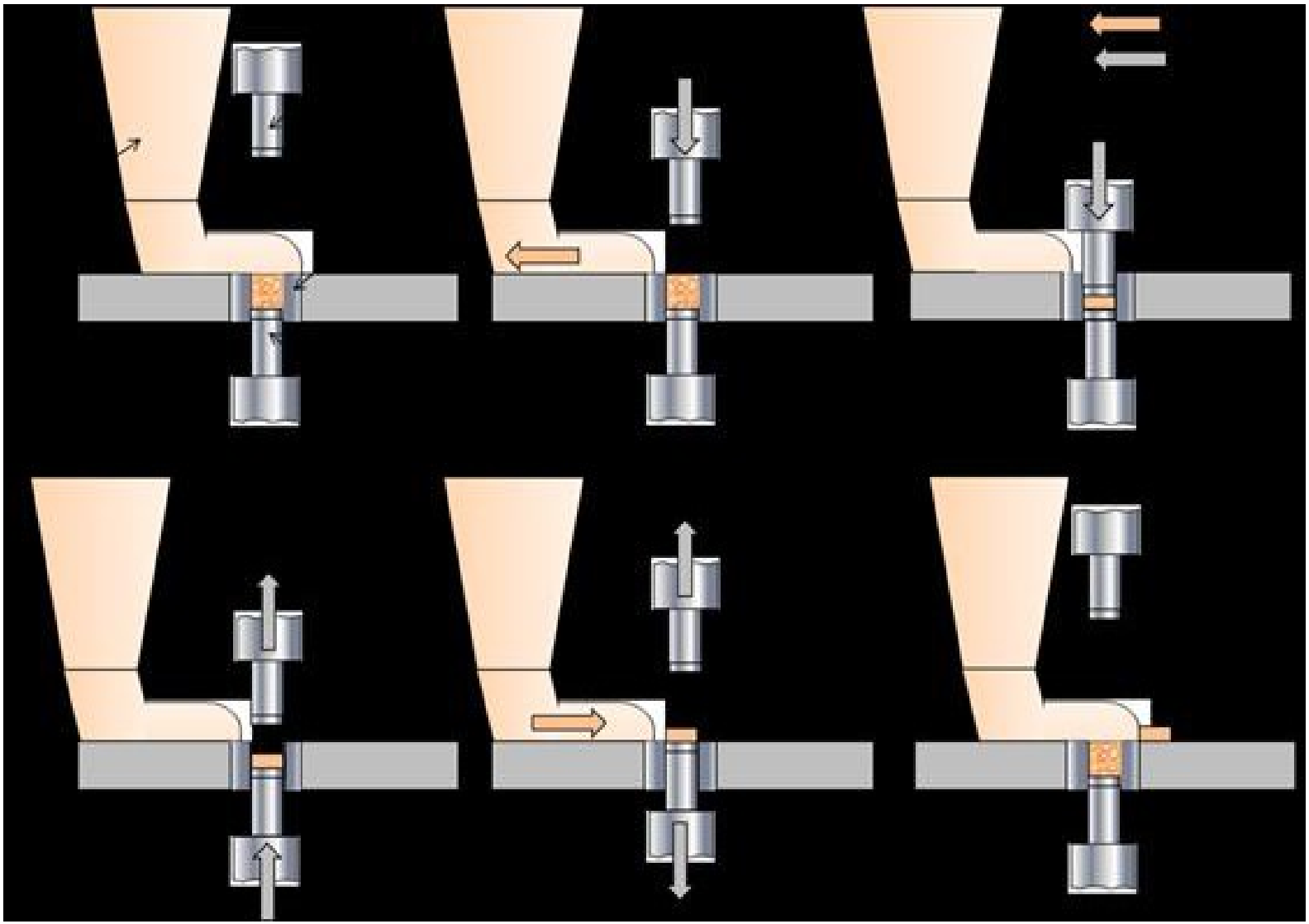
- Tablet manufacturing process includes weighing, milling, granulation and drying, blending and lubrication, compression and/or coating
- For a given formulation robust manufacturing process should be defined by evaluating all processing steps
- Process of tableting, called compaction cycle, can be divided into three stages :
    1. Die filling
    2. Compression [Compaction]
    3. Ejection

1. **Filling**: Lower punch falls in the die leaving a cavity into which granules flows under the influence a gravity from the hopper.
2. **Compression**: Upper punch, drops, and its tip enters the die. The porosity of the contents of the dies progressively reduced, and the particles are forced into the over closer proximity to each other.
3. **Ejection:** Upper punch is withdrawn from the die, lower punch rises upwards simultaneously feed shoe comes over die and moves the compressed tablet from the site.

Sequence of events involved in tabletting process


Die, surface view
Die, section
Lower punch
Position 1
Upper punch is raised; lower punch has dropped
Foot of hopper shoe
Granules
Position 2
Hopper shoe has moved forward over die and granules fall into die
Position 3
Hopper shoe has moved back. Upper punch has come down compressing granules into tablet
Position 4
Upper punch has moved upwards. Lower punch has moved upwards to eject tablet. The cycle is now repeated

Tablets compression processing steps



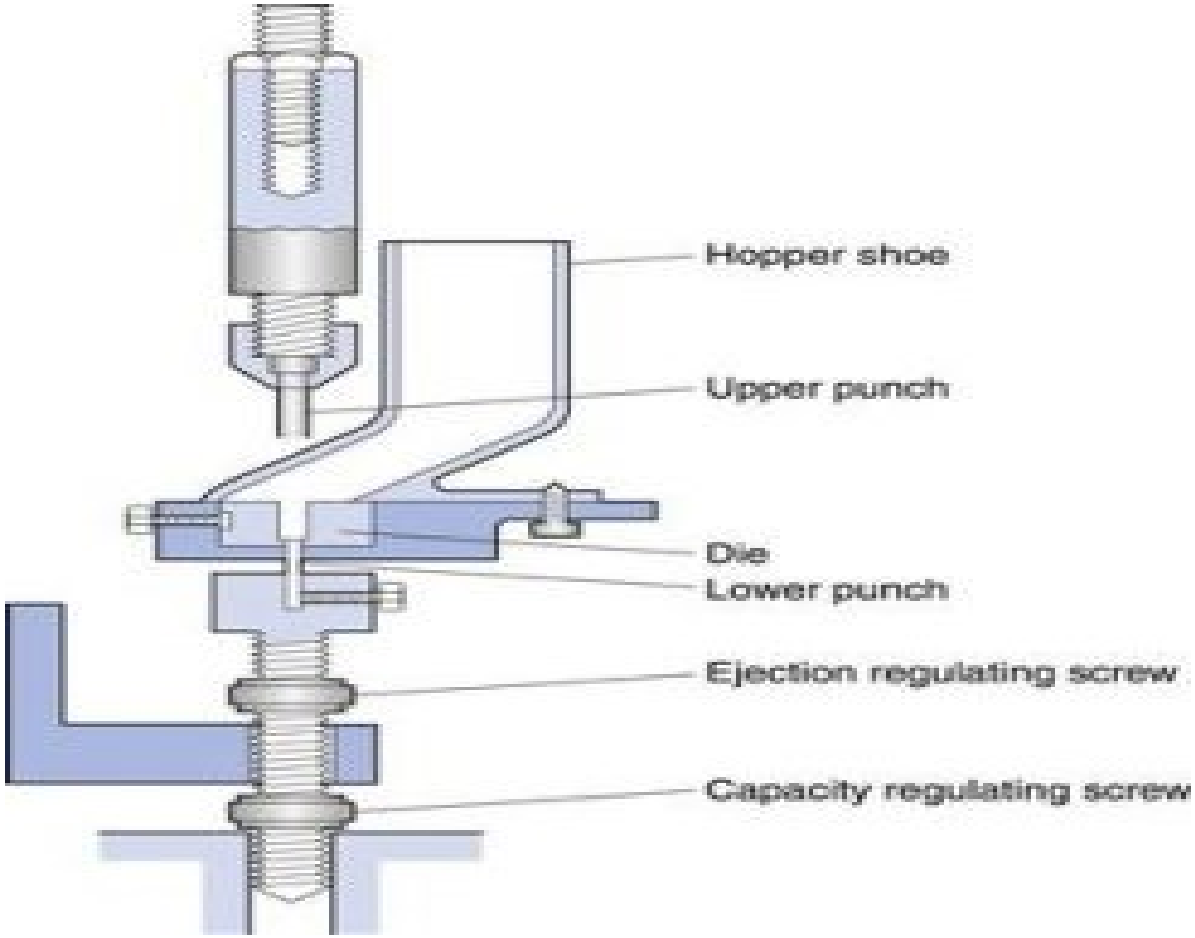
Tablet presses

There are two types of press in common use during tablet production:

1. Single-punch press [*eccentric press]*
2. Rotary press [*Multistation press*]

Single-punch press [eccentric press] [200 tablets/minute]

- Employs a single tooling station,i.e., possesses one die , one pair of punches & one hopper
- Powder is held in a hopper
- The hopper shoe moves to and fro over the die
- Powder is fed into the die by gravity when a hopper shoe is located over the die
- The position of the lower punch controls amount of powder filled into the die as it is made stationary
- When the hopper shoe is located beside the die, the upper punch descends &the powder is compressed
- The lower punch is stationary during compression & the pressure is thus applied by only upper punch, making the single punch machine a "stamping press"
- Tablet is ejected as lower punch moves up & removed by hopper shoe as it moves back to the die for next filling



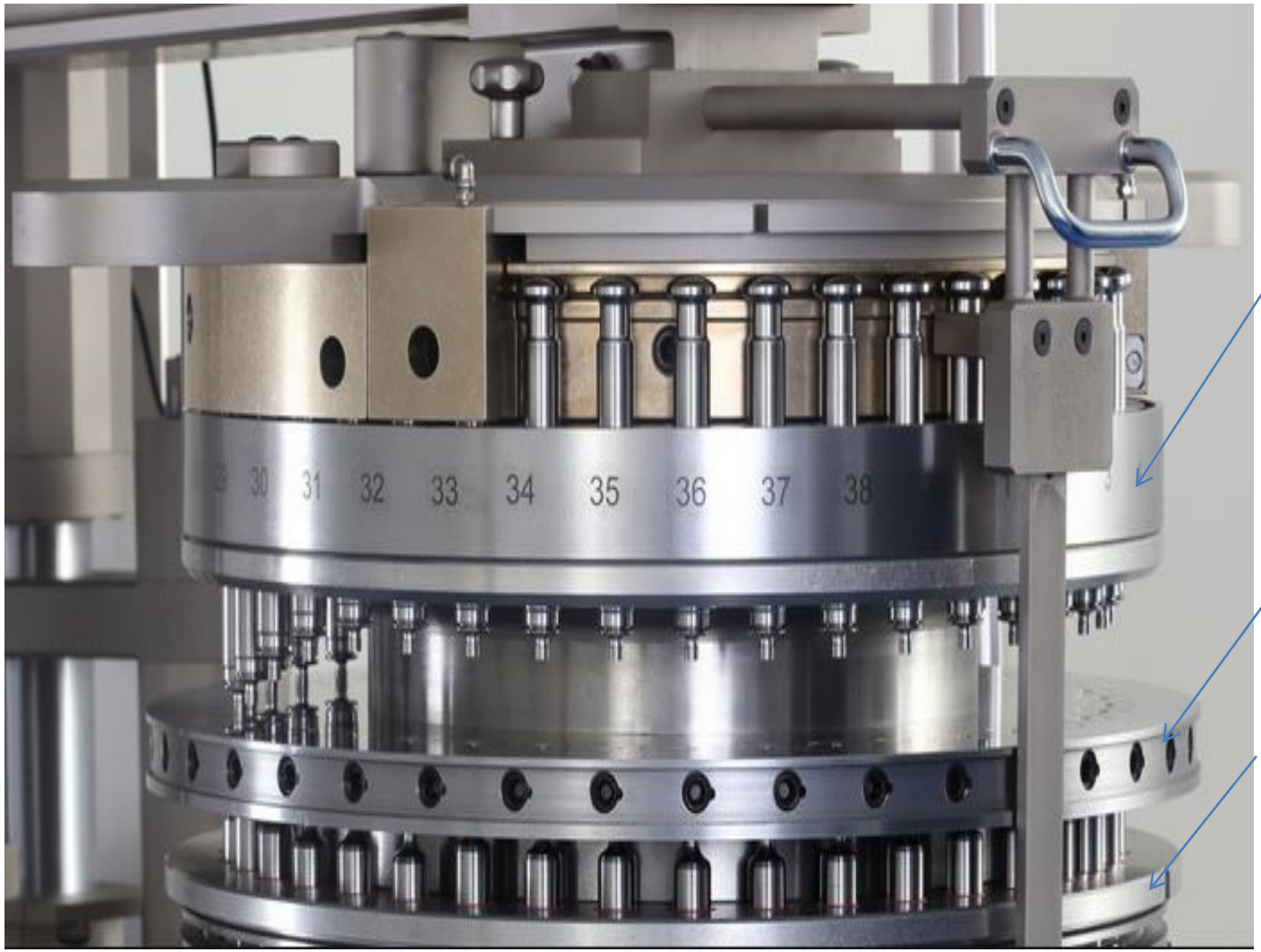
Single punch press

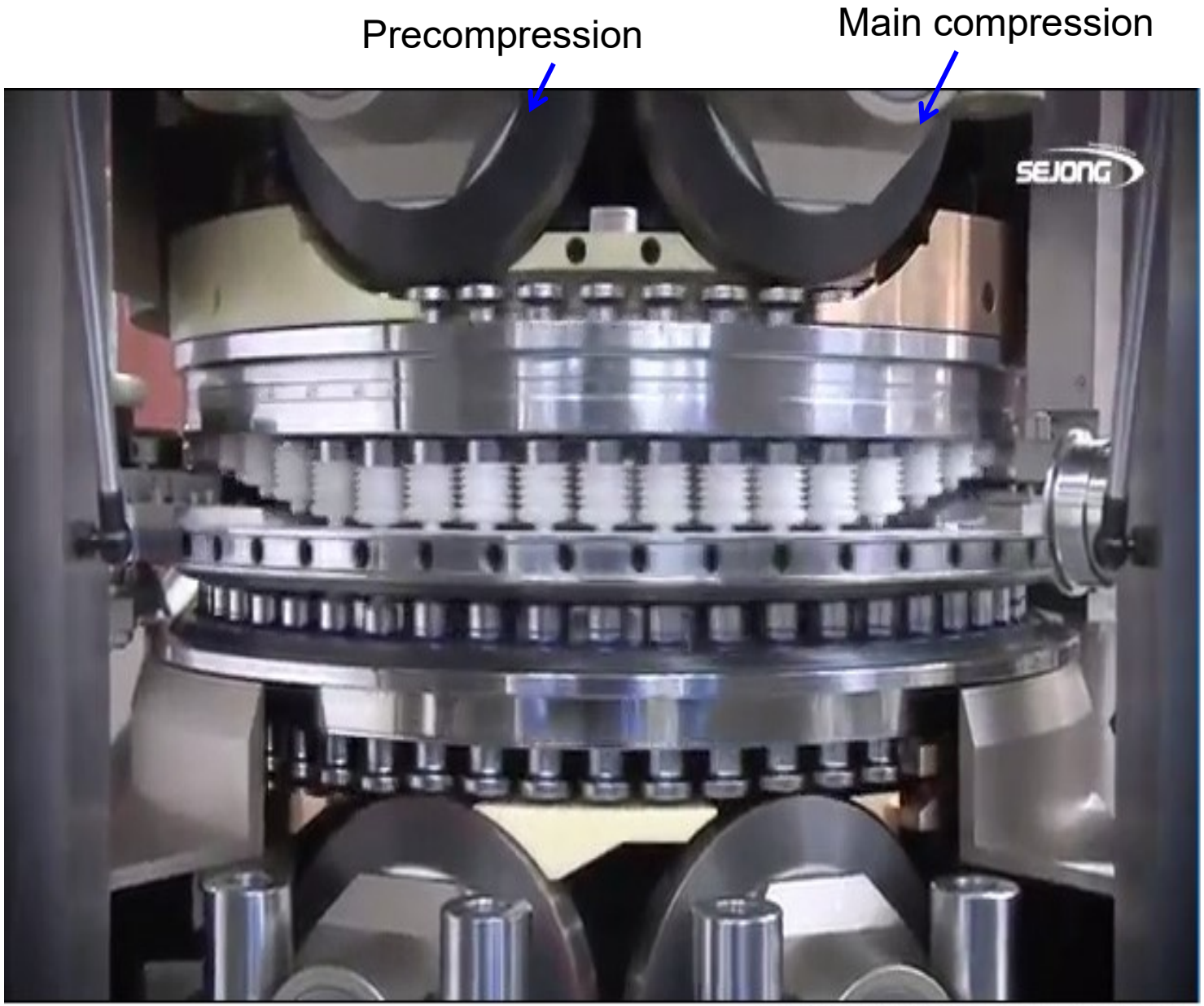
Advantages of single press

- The machine structure is simple and small,
- Very easy to operate
- Less noisy
- Takes lesser surface area

Rotary press [Multistation press]

- Has several punches and dies, one or more hopper
- Achieves high production rates [least 10,000 tablets per minute] by using many punch and die sets, fitted round the periphery of a turret[die table]
- Dies are filled at one or more points on the machine, and, as the turret rotates, the punch heads are brought, in turn, between pairs of stationary metal rollers
- Passing b/n the rollers, the punch heads are forced vertically together & exert a compressive force on the granulation in the dies b/n them
- Primarily used during scale-up & large scale production


30
31
32
33
34
35
36
37
38
Upper turret
Die table
Lower turret



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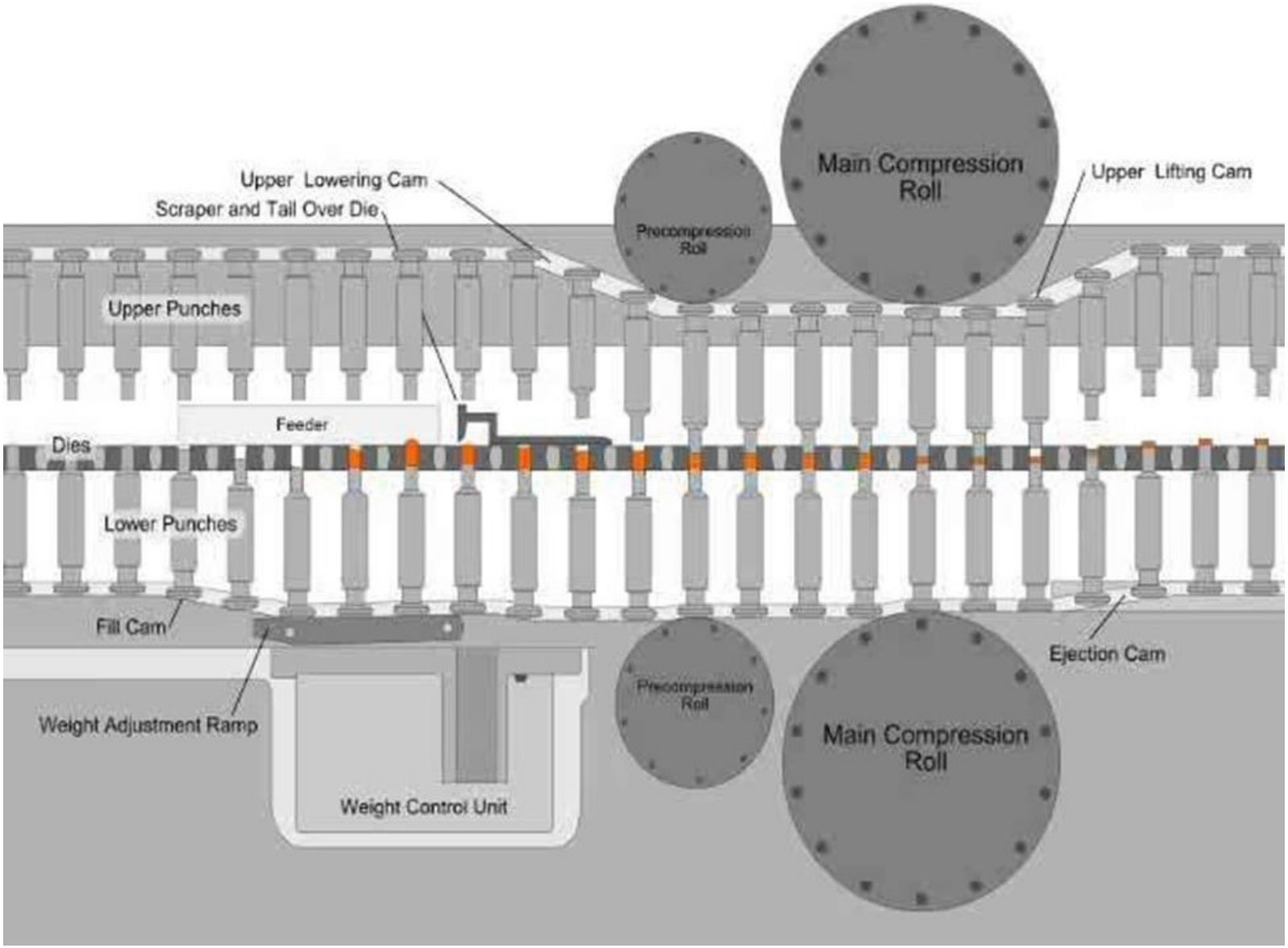
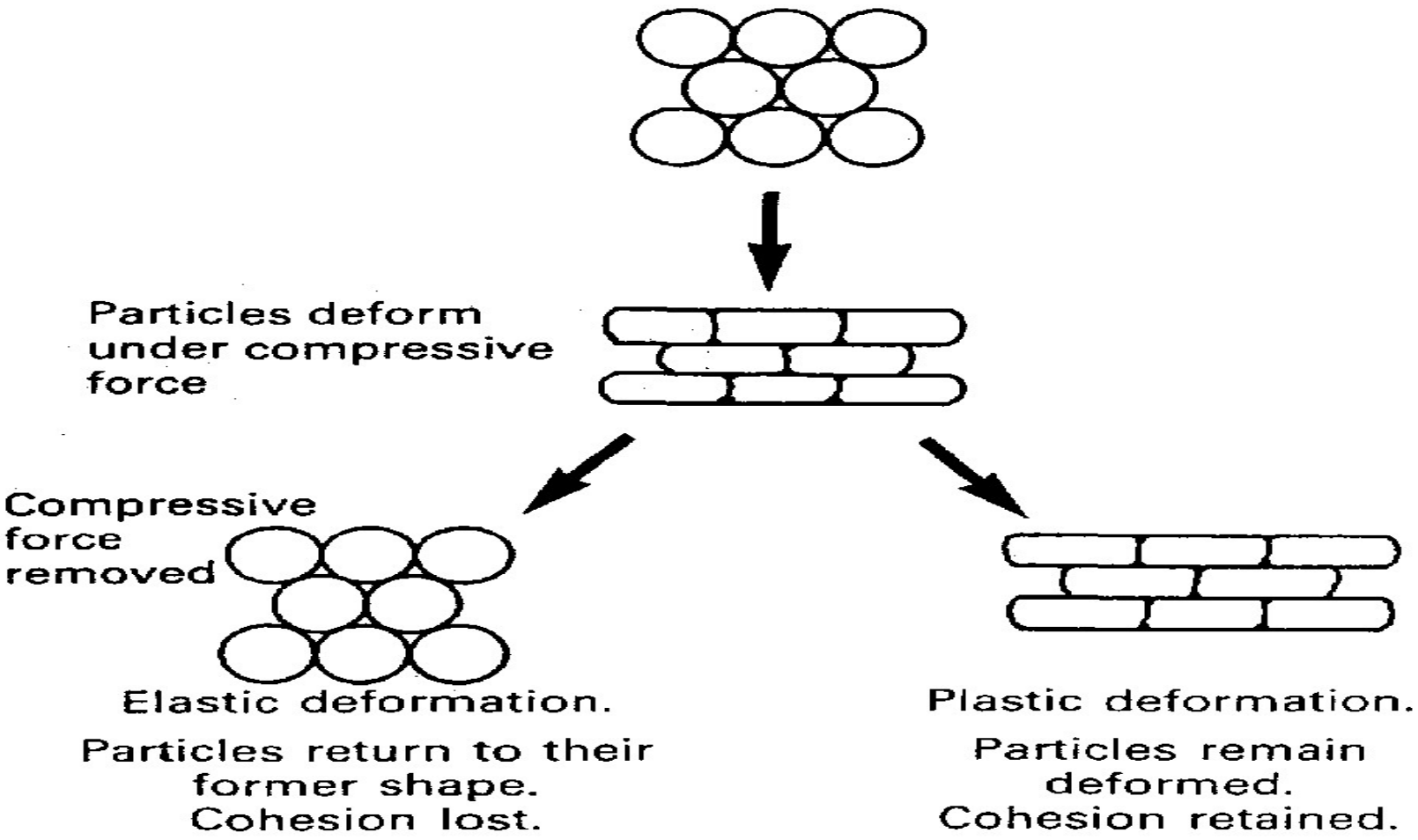


Rotary press

5.3. Fundamentals of powder compaction

- Powder or granules are compressed in to tablets following elastic or plastic deformation that results in particle-particle bond
- **Elastic deformation**: Densification of the particle due to a small movement of the cluster of molecules or ions that forms the particle, e.g. a crystal lattice or a cluster of disordered molecules
- Plastic deformation occurs by sliding of molecules along slip planes



Schematic illustration of particle deformation, elastic and plastic, during compression.

5.4. Types of Tablet

▪ Compressed tablets	▪ Coated tablets
▪ Multilayered tablets	➢ Sugar coated tablets
▪ Modified release tablets	➢ Film coated tablets
➢ Immediate release tablets	➢ Enteric coated tablets
➢ Controlled release tablets	▪ Oral cavity tablets
➢ Delayed release tablets	➢ Sublingual tablets
▪ Implants	➢ Buccal tablets
▪ Dispersible tablets	➢ Chewable tablets

5.4. Types of Tablet

- Based on their drug-release characteristics, tablets can be classified into three types

Immediate release tablets

- The most common type of tablet from which drug is released rapidly

Examples: Disintegrating, chewable, effervescent, sublingual and buccal tablets

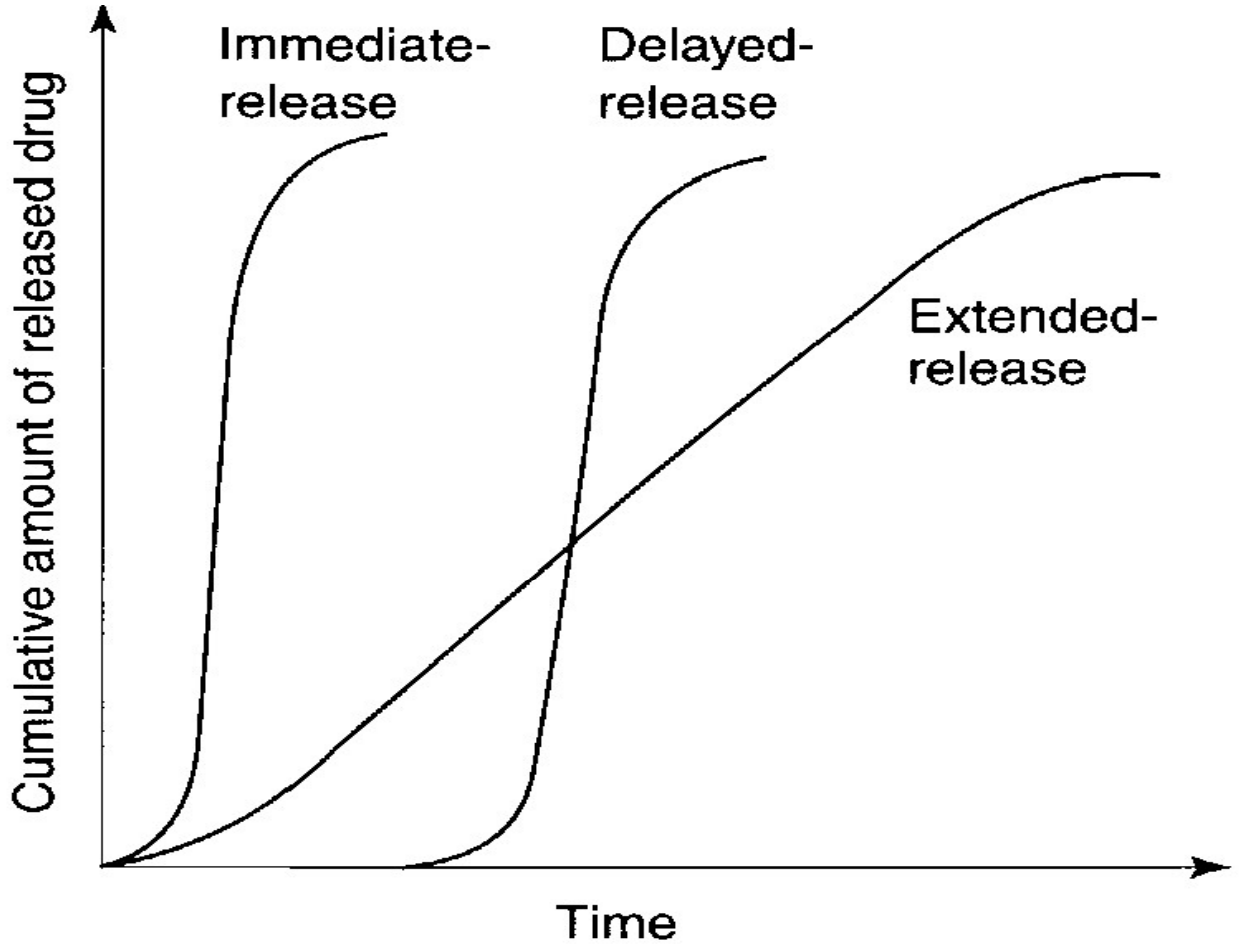
Modified-release tablets that are swallowed intact:

Extended-release tablet

- Drug is released slowly at a nearly constant rate over longer period of time

Delayed-release tablets

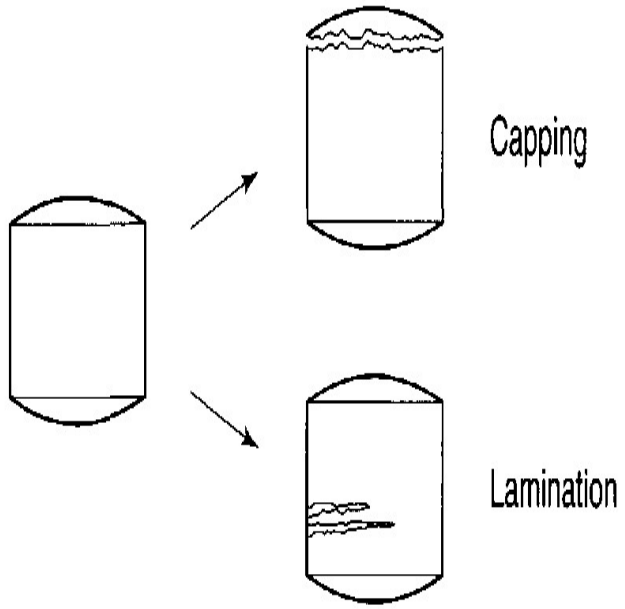
- Drug is released from such tablet as enteric coated tablet after some time is elapsed



Schematic representation of the cumulative amount of drug released from immediate-, extended- and delayed release tablets.

Tablet manufacturing problems

- Sticking / Picking: Adhesion of granules to punch face or die wall
- Cracking: Caused by out ward radiation of fracture on tablet surface
- Capping: Removal of tablet crown from its top &/ or bottom
- Lamination: Breakage of a tablet along its body



5.5. Tablet testing(QC)

- A fundamental quality attribute for all pharmaceutical preparations is the requirement for a constant dose of drug between individual tablets

Test parameters for tablet quality

1. Uniformity of weight & uniformity of active ingredient
2. Disintegration testing
3. Dissolution testing
4. Mechanical strength

Weight uniformity test

1. The test is carried out by collecting a sample of tablets, normally **20**, from a batch and determining their individual weights & average weight
2. Sample complies with t standard if individual weights do not deviate from mean more than is permitted in terms of percentage

Test for drug content uniformity

1. Carried out by collecting a sample of **10 tablets**, followed by a determination of amount of drug in each tablet & average drug content per tablet
2. Drug content of individual tablets should fall within specified limits in terms of % deviation from mean

Limit according to USP	
Average weight	**Permissible percentage limit**
< 130 mg	**±10**
[130 -324] mg	**±7.5**
>324 mg	**±5**

Disintegration testing

- Carried out by agitating **six tablets** in aqueous medium at a defined temperature
- The time to reach the end-point of the test is recorded
- The preparation complies with the test if the time to reach this end-point is below a given limit
- End-point of the test is the time at which all visible parts of the tablets are eliminated from a set of test tubes and no fragments of tablet remain on the screen
- Complete disintegration is defined as that state in which any residue of the unit, except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus or adhering to the lower surface of the disk, if used, is a soft mass having no palpably firm core

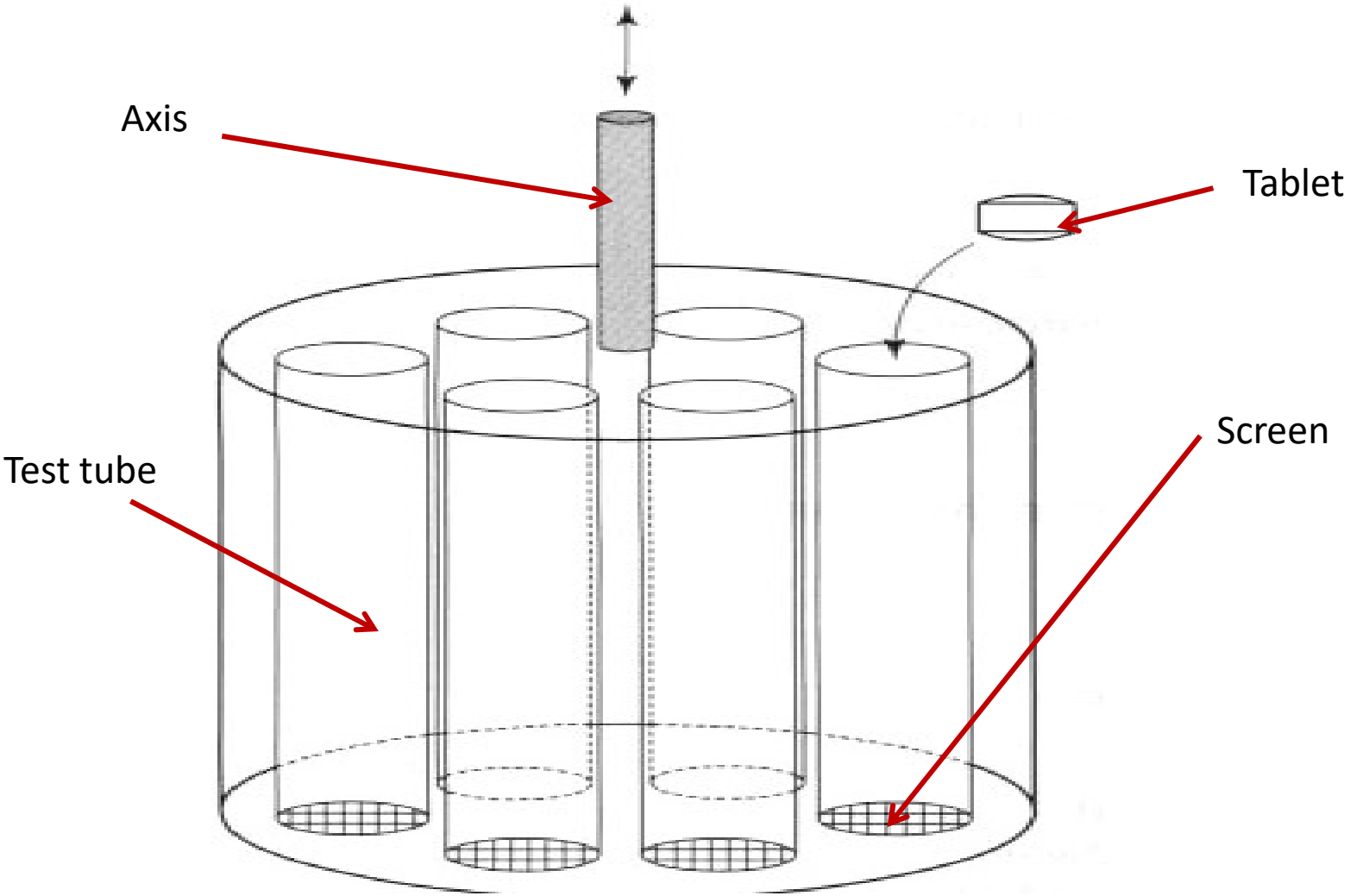


Diagram of a disintegration instrument for the testing of tablet disintegration time

Dissolution testing

- Used to study drug release pattern from a solid dosage form such as tablet

Reasons for conducting dissolution studies

1. To evaluate potential effect of formulation and process variables on drug bioavailability
2. To ensure that preparations comply with product specifications prior to market authorization
3. To verify batch-to-batch reproducibility
4. To indicate performance of a preparation under in vivo conditions

Note: In-vitro/in-vivo correlation is needed for № 4

Dissolution methods

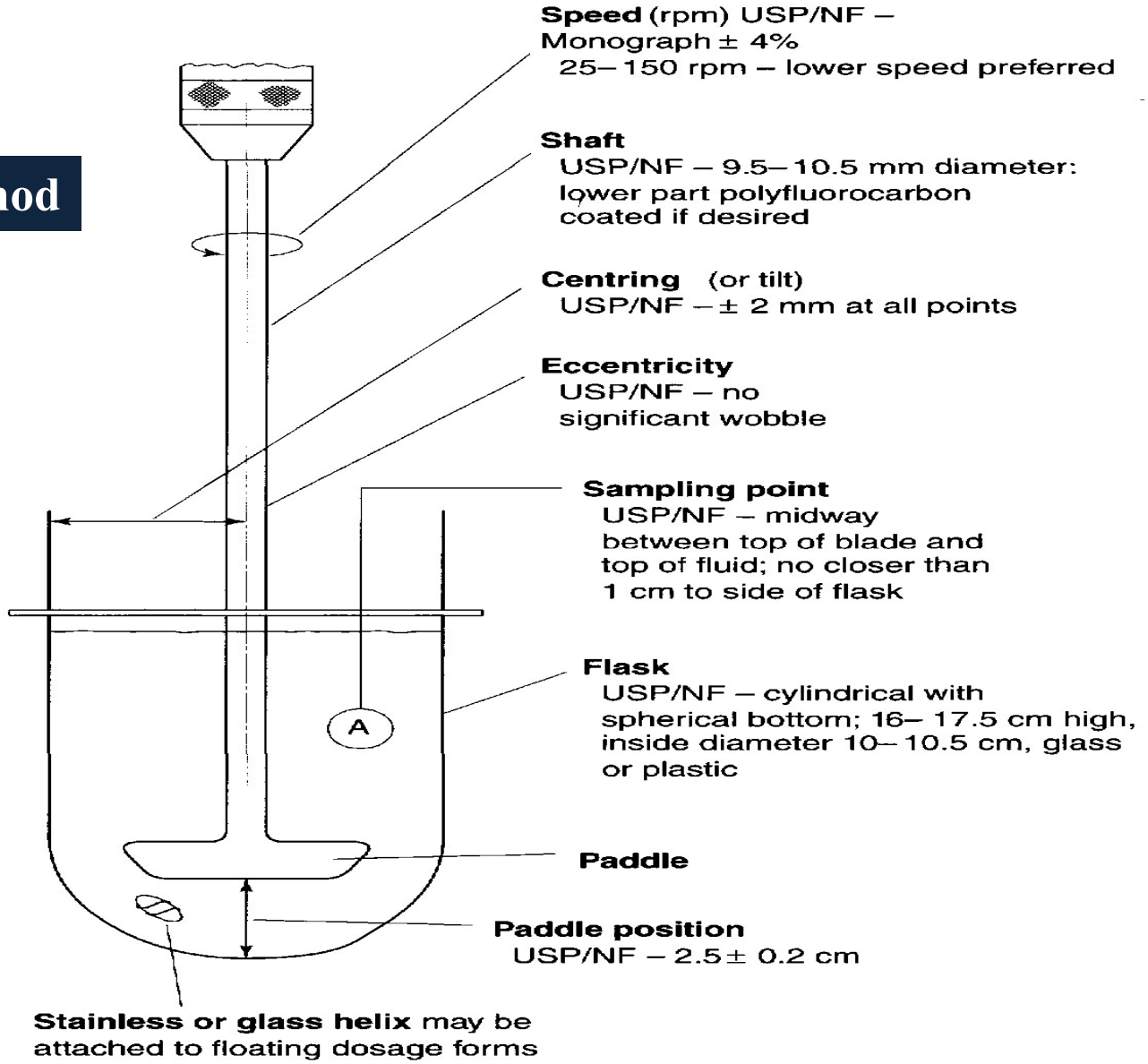
1. Stirred-vessel method

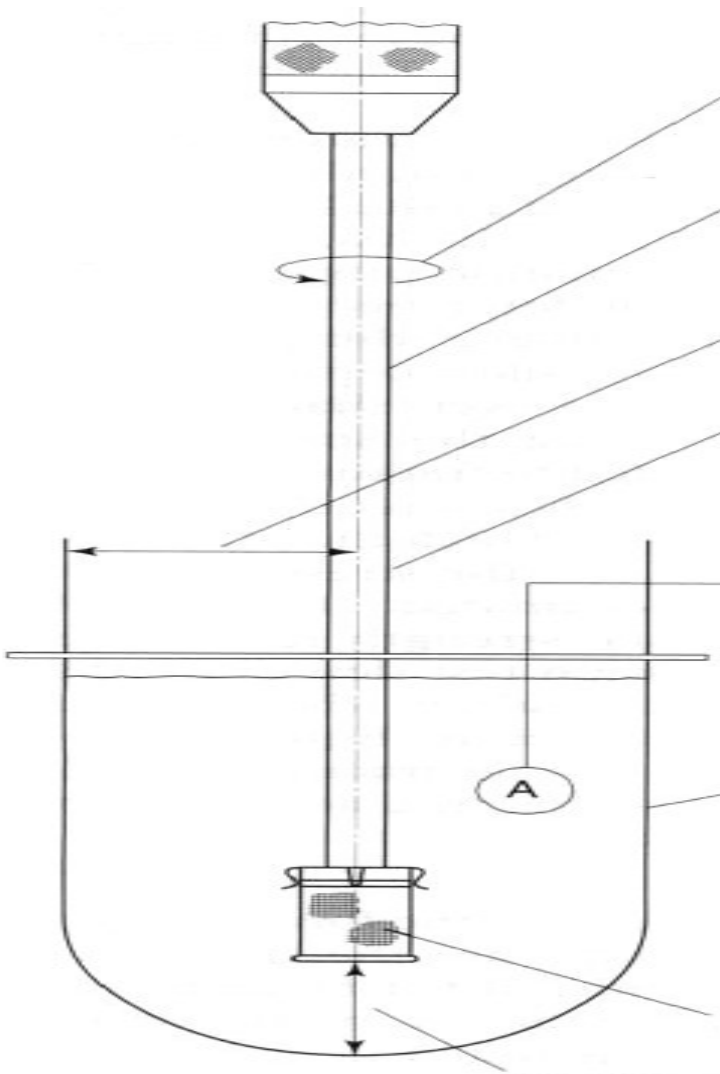
1.1. Paddle method: Tablet is placed in the vessel and the dissolution medium is agitated by a rotating paddle

1.2. Rotating-basket method

- Tablet is placed in a screened small basket
- Basket with the tablet is immersed in dissolution medium and rotated at a given speed

Paddle method


Speed (rpm) USP/NF – Monograph ± 4%
25–150 rpm – lower speed preferred
Shaft
USP/NF – 9.5–10.5 mm diameter: lower part polyfluorocarbon coated if desired
Centring (or tilt)
USP/NF – ± 2 mm at all points
Eccentricity
USP/NF – no significant wobble
Sampling point
USP/NF – midway between top of blade and top of fluid; no closer than 1 cm to side of flask
A
Flask
USP/NF – cylindrical with spherical bottom; 16–17.5 cm high, inside diameter 10–10.5 cm, glass or plastic
Paddle
Paddle position
USP/NF – 2.5 ± 0.2 cm
Stainless or glass helix may be attached to floating dosage forms



Speed (rpm) as specified in monograph
25 –150 rpm (± 4% USP/NF, ± 5% BP)

Shaft
USP/NF – 6– 10.5 mm diameter;
BP – approximately 6 mm diameter;
2 mm vent in disc drive

Centring (or tilt)
± 2 mm at all points

Eccentricity
USP/NF – no significant wobble;
BP – no perceptible wobble

Sampling point
USP/NF – midway from top of basket to top of fluid and no closer than 1 cm to side of flask
BP – halfway between basket and side at middle of basket

Flask
USP/NF – cylindrical with spherical bottom; 16– 17.5 cm high, inside diameter 10– 10.5 cm, plastic or glass
BP – cylindrical, flat bottomed, glass

Basket

Basket position
USP/NF – 2.5 ± 0.2 cm
BP – 2.0 ± 0.2 cm

Rotating-basket method

Continuous-flow methods

- ❖ The preparation is held within a flow cell, through which the dissolution medium is pumped at a controlled rate from a large reservoir.
- ❖ The liquid which has passed the flow cell is collected for analysis of drug content.

Note

- Continuous-flow cell method has advantage over stirred-vessel method as it maintains **sink conditions** throughout the experiment and **avoids floating of the preparation**

Mechanical strength testing

- Attrition-resistance & fracture-resistance methods are the most commonly used tablet strength testing methods

Attrition-resistance method [Friability test]

i. **Ten tablets** of known weights are placed in the friability tester and subjected to combined effects of abrasion and shock by making the plastic chamber to revolve at 20 rpm for 5 minutes

ii. The tablets are de-dusted, reweighed

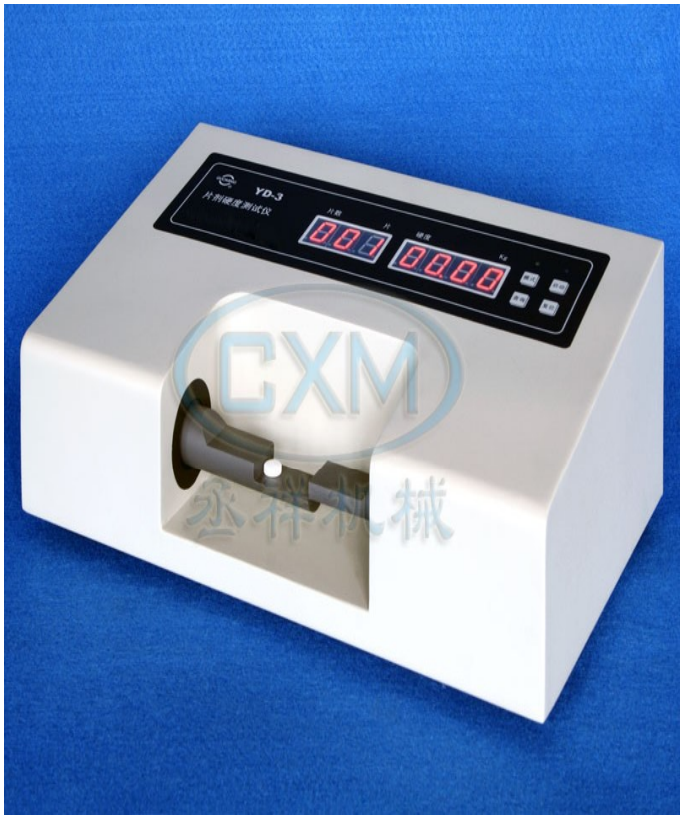
iii. percent loss in weight is recorded as friability.

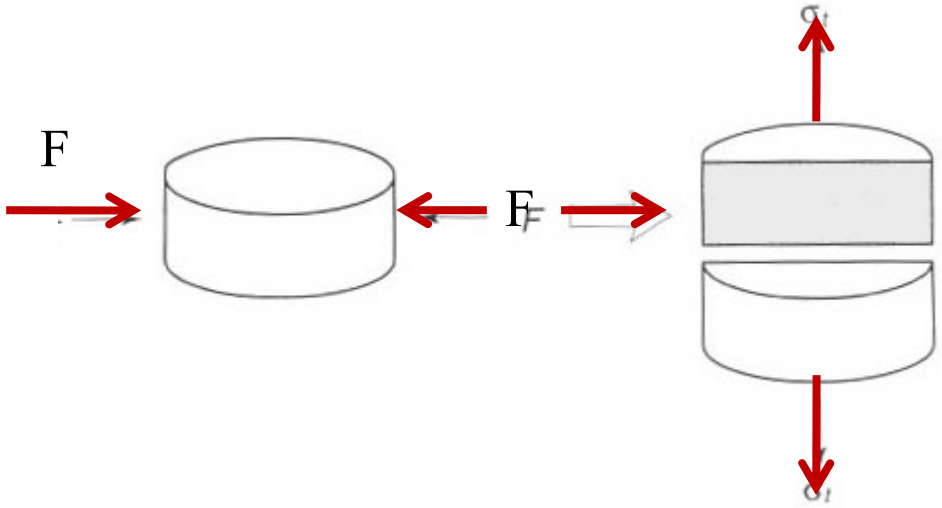
iv. The test is accepted if percent weight loss < 1%

Note: Occurrence of capping or lamination during testing leads to test rejection

Fracture-resistance method [Hardness test]

Tablet hardness tester is instrument for detecting & recording force that crush tablet along its diameter





6. Tablet Coating

6.1. Tablet coating principles

6.2. Coating process and equipment

6.3. Sugar coating and film coating

6.4. Coating formula optimization

6.5. Quality control

Tablet coating : Application of a coating material to the exterior of a compressed tablet

Major reasons why tablets are coated

- To protect ingredients from environmental impacts such as light and moisture
- To mask bitter or unpleasant tastes
- To facilitate tablet swallowing
- To avoid mottling and improve tablet elegance
- To facilitate product identification
- To impart tensile strength to tablets
- to impart enteric or controlled-release properties to the coated tablet by using functional film coatings

Main types of tablet coating [2]

1. Film coating

2. Sugar coating

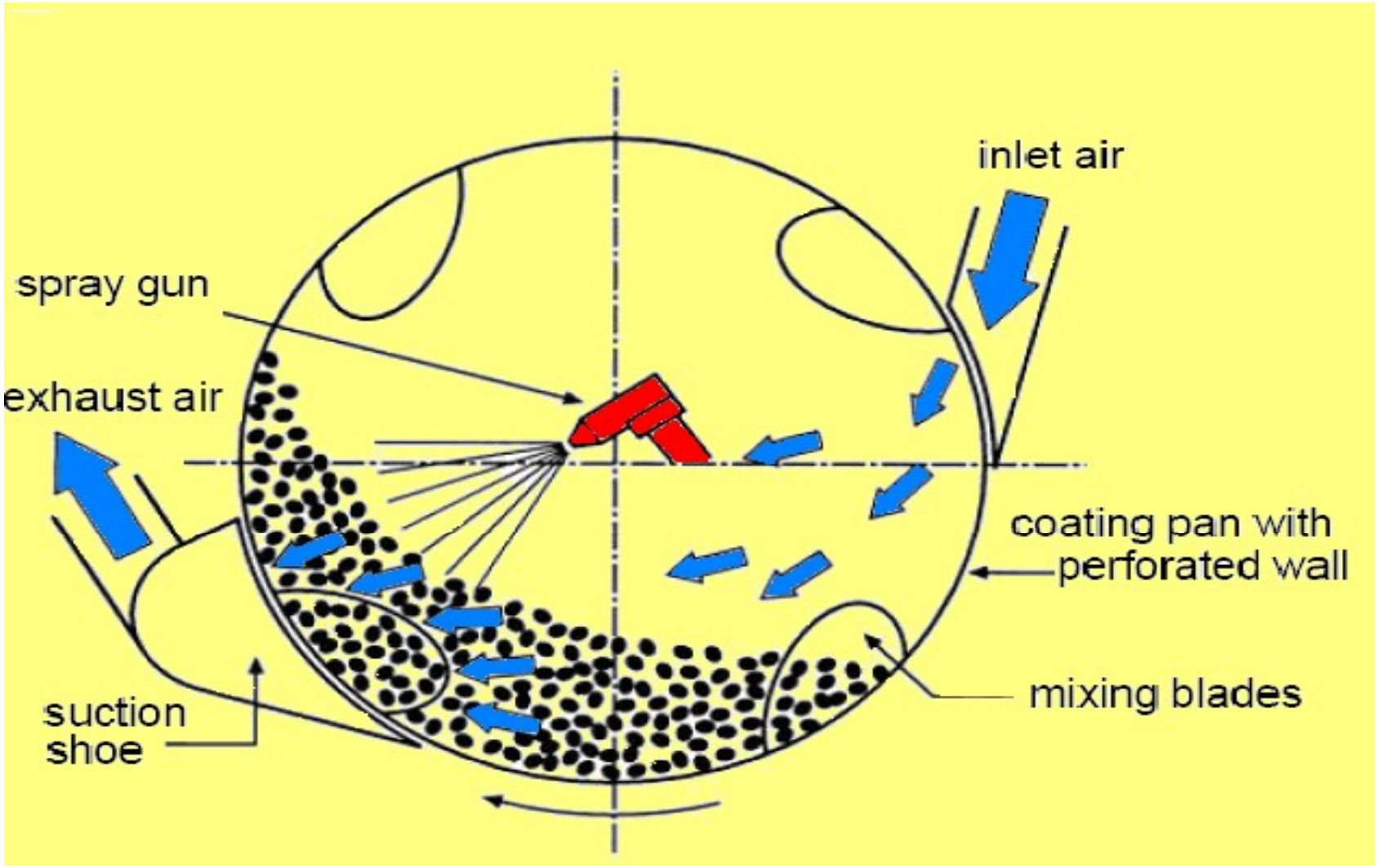
Process description

- Film coating involves deposition of a thin film of polymer surrounding tablet core by a spray method
- Film coating is a single stage process, which involves spraying a coating solution onto surface of tables

Components of film coating solution

1. Polymer
2. Solvent
3. Plasticizer
4. Colourant

The solution is sprayed onto a rotating tablet bed followed by drying, which facilitates the removal of the solvent leaving behind the deposition of thin film of coating materials around each tablet.



Accela Cota [Film coating machine]

Ideal characteristics of a film coating Polymer

- Solubility: For conventional film coating, polymer should have good solubility to facilitate drug release from tablet
- For a modified release, polymer system of low water solubility or permeability should be chosen
- Viscosity: Polymers with low viscosity permit easy, trouble-free spraying of their solutions on to tablet
- Permeability: Polymers with efficient barrier against permeability to water vapour or atmospheric gases optimizes tablet shelf-life
- Mechanical strength: Coating polymers must give adequate strength to withstand impact & abrasion encountered in normal handling. Insufficient coating strength is disclosed by coating imperfections

Plasticizers : Decrease film brittleness

Examples

- Polyols, such as polyethylene glycol 400
- Organic esters, such as diethyl phthalate oils/ glycerides, such as fractionated coconut oil

Note: In general, only water-miscible plasticizers can be used for aqueous-based spray systems.

Colourants: Invariably water-insoluble pigments are used

Examples

- Iron oxide pigments
- Titanium dioxide
- Aluminium Lakes

Polymers used for film coating

1. **Cellulose derivatives**
   - Hydroxypropyl methylcellulose: Most commonly used
   - Methylcellulose
   - Hydroxypropylcellulose

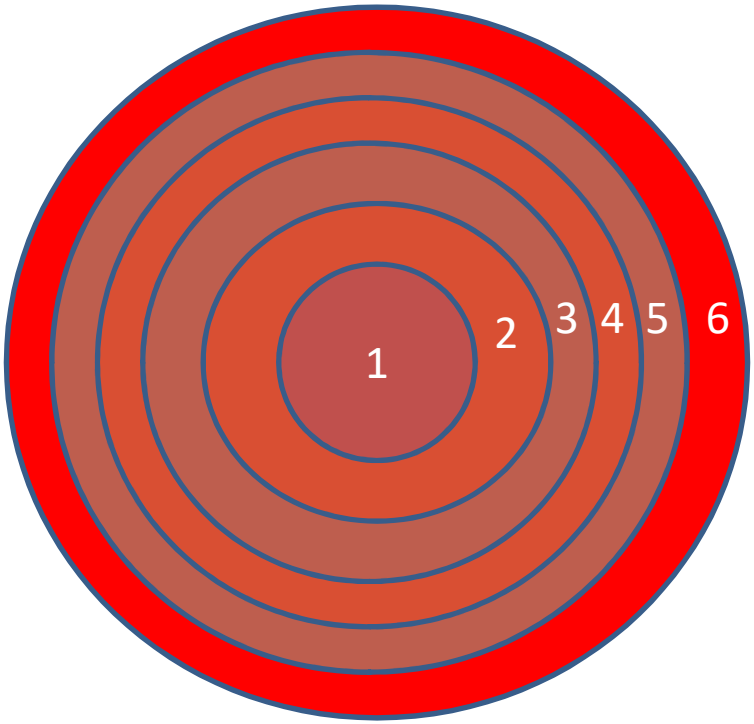
2. Methacrylate amino ester copolymers

- Insoluble in aqueous media below pH 4 but in neutral or alkaline media the films achieve solubility by swelling and increased permeability.
- Used for delayed - release formulations

- Cellulose acetate phthalate [CAP]
- Ethyl cellulose

Sugar coating

- Traditionally, sugar coatings formed the bulk of coated tablets but today film coatings are the more modern technology in tablet coating.
- **Description of tablets:** Smooth, rounded and polished to a high gloss
- **Process:** Multistage process involving 6 separate operations



Key

1. Seal coat
2. Subcoat
3. Smoothing
4. Couloring
5. Polishing
6. Printing

Multistage process

1. **Sealing tablet core:** Water impermeable polymer such as Shellac, cellulose acetate phthalate and polyvinyl acetate phthalate is applied to protect the core from moisture, thus increasing its shelf life.
2. **Sub coating**: by adding bulking agents such as calcium carbonate or talc in combination with sucrose solution
3. **Smoothing process**: remove rough layers formed in step 2 with the application of sucrose syrup
4. **Colouring**: for aesthetic purposes often titanium based pigments are included
5. **Polishing** :to give characteristic shine, commonly using beeswax, carnauba wax

Comparison of sugar & film coatings

Film coating

Tablet appearance

- ✓ Retains shape of original core
- ✓ Small weight increase of 2-3% due to coating material
- ✓ logo or 'break lines' possible

Process

- ✓ Can be automated e.g. **Accela Cota**
- ✓ Easy training operation
- ✓ Single stage process
- ✓ Easily adaptable for controlled release allows for functional coatings.

Sugar coating

Tablet appearance

- ✓ Rounded with high degree of polish
- ✓ Larger weight increase 30-50% due to coating material
- ✓ Logo or 'break lines' are impossible

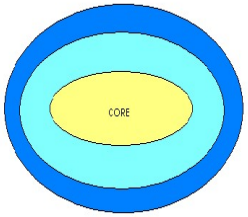
Process

- ✓ Difficult to automate e.g. traditional coating pan
- ✓ Considerable training operation required
- ✓ Multistage process
- ✓ Not able to be used for controlled release apart from enteric coating.

Coating formula optimization

- Adequate means of atomizing the spray liquid for application to the tablet cores
- Adequate mixing and agitation of the tablet bed since unlike sugar coat, spray coating relies upon each core passing via the area of spraying
- Sufficient heat input in the form of drying air to provide the latent heat of evaporation of the solvent. This is particularly important with aqueous-based spraying
- Good exhaust facilities to remove dust- and solvent-laden air

Press coating



- Involves compaction of material around preformed core
- Used for physical separation of incompatible ingredients
- Produce a repeat - action product
- Provides immediate & a slow - release component
- Release rates can be controlled by modification of the geometry, core composition & inclusion of a membrane layer

- **Press coating** differs from sugar and film coating process since it enables incompatible materials to be formulated together, such that one chemical or more is placed in the core and the other (s) in the coating material
- **Press coating** involves using a preliminary compression step to produce a relatively soft tablet core which is then placed in a large die containing coating material. Further coating material is added & the content compressed. A similar light compression is used for the production of layers and a final main compression step used to bind the layers together

Quality control

- European Pharmacopoeia has similar requirements for coated and uncoated tablets, the differences being:
- Film-coated tablets must comply with uniformity of mass test *unless otherwise justified and authorized*
- Film-coated tablets comply with the disintegration test for uncoated tablets except that the apparatus is operated for 30 minutes.
- The requirement for coated tablets other than film coated is modified to include a 60-minute operating time. Furthermore, the test may be repeated using 0.1 N HC1 in the event that any tablets fail to disintegrate in the presence of water

Write True or False & give reason(s) for each answer

1. Coated & conventional tablets disclose same range of disintegration time
2. Dry & wet granulations are applicable to drugs having identical sensitivity to their environment
3. Lyophilized antibiotics are compatible with their environment, thus need no special packing & sealing procedures
4. Enteric coated tablets starts releasing drug into gastric content but drug absorption commence from duodenum
5. Tablet ejection stage is preceded by movements of upper & lower punches in opposite directions
6. Press coated tablets involve deposition of coating polymer on conventional tablets

Unit 7: Capsules

7.1. Hard gelatin capsules

7.1.1. Raw materials used to make gelatin capsule

7.1.2. Manufacturing [equipments, empty capsule, filling (powder, semisolid, solid, liquid)]

7.1.3. Formulation

Powder formulation, formulation for filling, formulation for release of API, formulation for position release

7.1.4. Quality control

7.2. Soft gelatin capsules

- Description of soft gel, rationale for selection of soft gel, Manufacture of soft gel (formulation and product QC)

7.1. Introduction

- Capsules are solid oral dosage forms in which drug is enclosed within empty hard or soft gelatin shell
- Hard gelatin capsules are rigid two - piece capsules that are manufactured in one procedure & filled in another totally separate operation, whereas formulation of soft gelatin capsules is more complex but all steps are integrated, i.e., production of empty soft gelatin shell & its filling operations are synchronized.
- In recent years hard capsules have been manufactured from hydroxypropyl methylcellulose in order to produce a shell with a low moisture content

7.1.1. Raw materials for empty gelatin capsule manufacture

1. Gelatin
2. Water
3. Colourants
4. Process aids
5. Preservatives [optional]
6. Plasticizers [exclusive to soft gelatin]

Common to both hard & soft empty gelatin capsules

Colourants

- Most commonly used colourants are non-azo dyes, not azo-dyes[-N=N-] since they are carcinogenic & triggers asthma attack and allergic reactions in sensitive individuals
- The three most widely used non-azo dyes are quinoline yellow, erythrosine & indigo -carmine
- The two types of pigments in use are : iron oxides [black, red and yellow], and titanium dioxide which is white and used to make the capsule opaque
- In the last few years there has been a move away from soluble dyes to water insoluble pigments, particularly the iron oxides, because they are not absorbed on ingestion

Process aids:

Wetting agent such as 0.5% Sodium lauryl sulfate is recommended by USNF for use in hard gelatin capsule manufacture to ensure that the lubricated metal moulds are uniformly covered when dipped into gelatin solution

Preservatives no more in use currently in finished hard gelatine capsule since its moisture content is 13-16% w/w and strongly bonded to gelatin molecule hence never support microbial growth but adequate to act as a plasticizer

Gelatin: is the major component of the empty capsule

- Gelatin is a generic term for a mixture of purified protein fractions obtained either by partial acid hydrolysis (type A gelatin) or by partial alkaline hydrolysis (type B gelatin) of animal collagen.
- Type A normally originates from porcine skin while type B is from animal bones
- Mixtures of type A & B are used to optimize desired characteristics of empty capsule with bone gelatin imparting firmness while porcine skin gelatin providing plasticity
- Isoelectric points for type A and type B gelatin are 7.0 – 9.0 & 4.8 – 5.0, respectively

- Properties of gelatin that are most important to capsule manufacturers are bloom strength & viscosity

Bloom or gel strength

- It is a measure of gelatin rigidity or cohesive strength of inetr-gelatin-molecules cross-linking which is proportional to molecular weight of gelatin
- Determined by Bloom gelometer that measures weight in grams required to move a 0.5 inch or 12.7 mm diameter plastic plunger 4mm into a 6.67% gelatin gel held at 10°C for 17hrs without breaking
- The unit of bloom is grams and its optimal value for hard gelatin gel is 200-200 g while for soft gelatin it is in the range 150-250 g

Viscosity

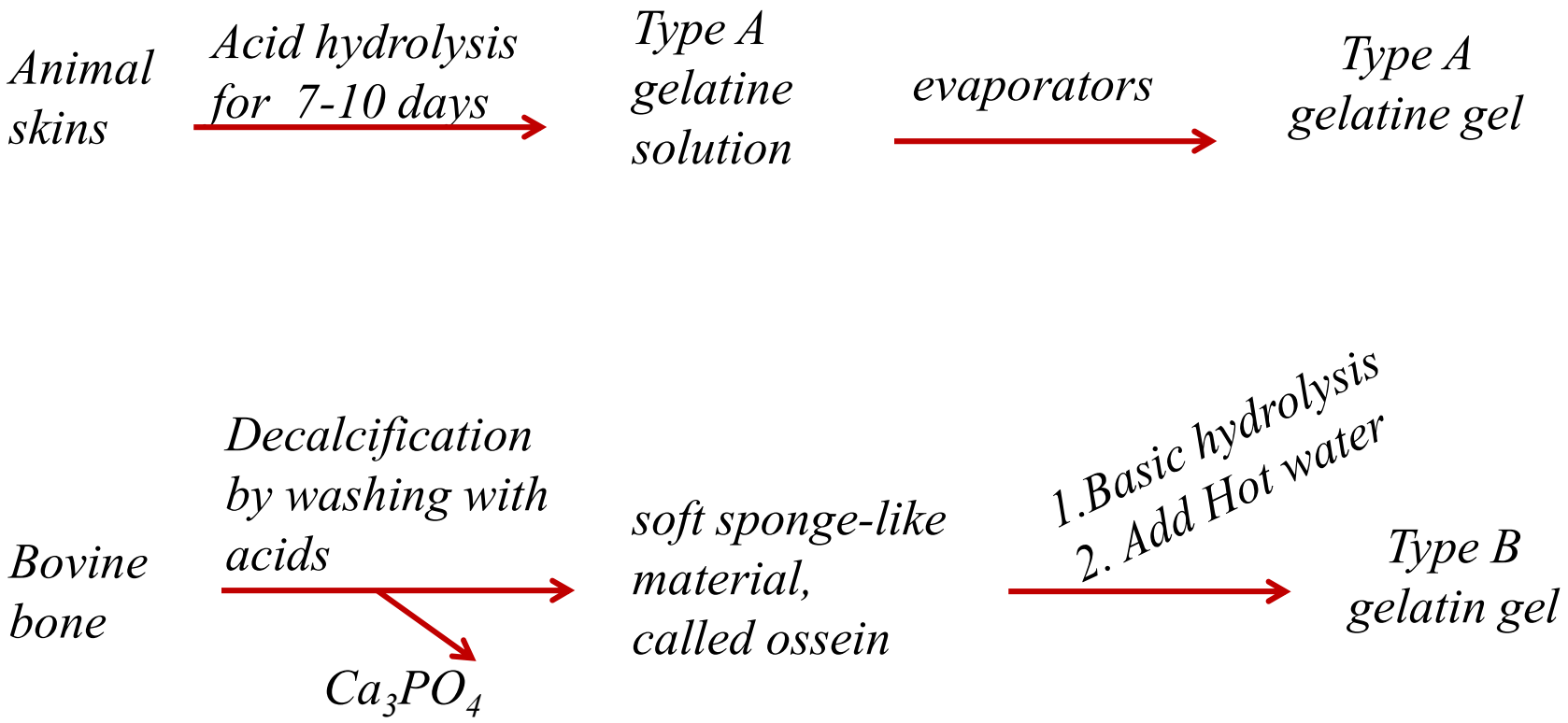
- It is a measure of the molecular chain length of gelatin
- It determines manufacturing characteristics of gelatin film
- It is measured in viscometer
- Determined on 6.67 % conc. of gelatin in water at 60 °C
- Standard viscosity value is in the range 25-45 millipoise

Characteristics of gelatin

- Non-toxic
- Readily soluble in biological fluids at body temp
- Produce strong flexible film with a wall thickness of about 100 μm
- Gelatin solution of high concentration, 40% w/v, is mobile at 50°C while that of other biological polymers, such as agar, are not
- A solution in water or in a water-plasticizer blend undergoes a reversible change from a sol –to- gel at temperatures only a few degrees above ambient

7.1.2. Manufacturing of empty capsule

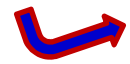
A. Manufacturing of hard gelatin empty capsule



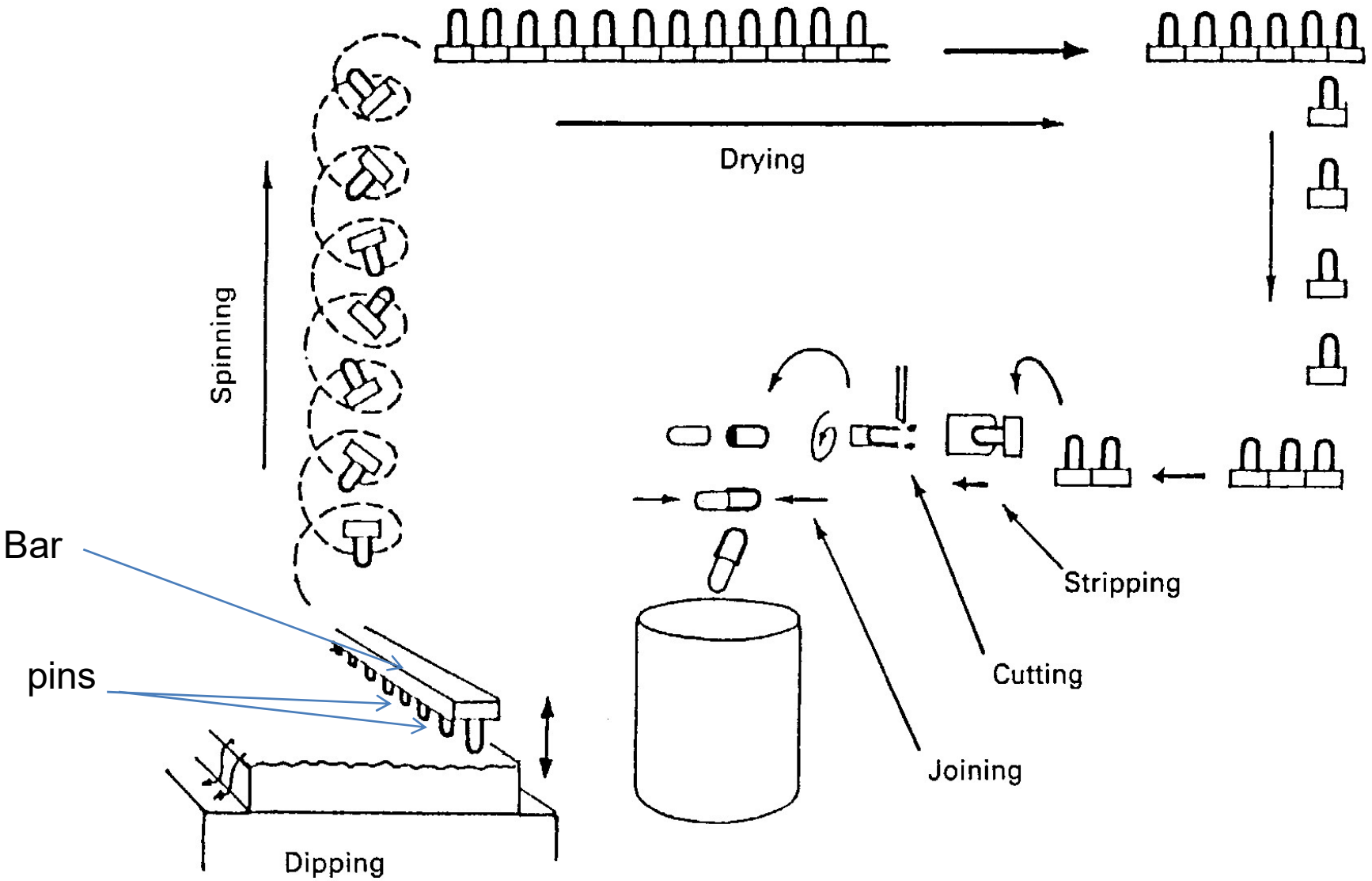
Procedure

1. Prepare concentrated gelatin solution, 35-40%, using demineralized hot H_2O, 60-70 °C, in jacketed pressure vessel
2. Apply vacuum to remove entrapped air bubbles from gelatin solution
3. Prepare aliquot parts of gelatin solution for the cap and body; add dye solutions & pigment suspensions to aliquot parts of the bulk solution
4. Measure viscosity of solution and make adjustment to target value to control shell thickness

Reason: Higher solution viscosity produces thicker shell wall while lower viscosity produces thinner shell wall

5. Transfer mixed solution to heated hot holding hopper on production machine equipped with 40,000 mould pins
6. Produce capsule shell using production machine having two mirror image parts, each for cap and body
7. Keep a fixed quantity of gelatin at 45° - 55°C in hopper, called a 'dip pan' or 'pot'
8. Produce capsules by dipping sets of moulds [22°C] into solution so that a film is formed on the surface of each mould by gelling
9. Withdraw the moulds slowly from the solution and subject them to spinning, drying, etc as shown 

Sequence of two-piece hard gelatin capsule shell manufacture



Properties of EHGC

- Its standard moisture content that act as a plasticizer is 13 – 16% w/w
- In env't with RH <13%, loss moisture & become brittle
- In environment with RH>16%, they gain moisture from their environment & become soft, tacky
- Easily soluble in water at 37 ^{O}C, below 37 ^{O}C their dissolution rate decline. Thus, both dissolution & disintegration test must be conducted at 37 ^{O}C
- Below 30 ^{O}C , HGC are insoluble, absorb water, swell & distorted
- HPMC capsules have a different solubility profile, being soluble at temperatures as low as 10°C

Filling of Empty Hard - Gelatin Capsule

- Filling materials must be compatible with gelatin shell
  - **Dry solids** [powders, granules, pellets, tablets]
  - **Semisolids** [Thermosoftening mixtures, thixotropic mixtures , pastes]
  - **Non-aqueous liquids** [oily liquids, non thixotropic mixtures]

Materials incompatible with capsule shell include:

- ❖ Moisture - sensitive drugs since moisture of empty gelatine capsule shell is 13-16% w/w
- ❖ All ingredients need to be free of trace amounts of formaldehyde to minimize cross - linking of gelatin
- ❖ Deliquescent or hygroscopic materials

- There are eight standard **capsule sizes**, of which the largest for oral use is size 0.
- The standard industrial sizes in use today for human medicines are from 0 to 4
- Prior to filling, the capsule shells that are added to the hopper flow via tube to reach capsule rectification station where caps are removed & bodies are filled with fill material and then recapped by the machine toward the end of filling station

Capsule size & corresponding volume or fill weight		
Capsule Size	**Volume (ml)**	**Fill weight (g)**
000	1.37	1.096
00	0.95	0.760
0	0.68	0.544
1	0.50	0.400
2	0.37	0.296
3	0.30	0.240
4	0.21	0.168
5	0.13	0.104

EHGC filling operation

Before conducting filling operation determine:

- Capsule size
- Types of formulation to be filled
- Fill weight of solid formulation

Fill weight = Body volume X body tapped density

- If tapped density of powder formulation is 0.5 gm/ml & capsule fill weight is 0.240 gm, find capsule size & body volume
- Fill weight of liquid formulation

Fill weight = specific gravity of liquid X capsule body volume X 0.8

- If sp.gravity of liquid formulation is 2 & capsule body volume is 0.28 ml, determine capsule size & formulation fill weight

Formulation to be filed into EHGC must:

- Give uniform fill
- Give stable product
- Release its active ingredient as intended
- Comply with pharmacopeia specifications
  - Disintegration time
  - Dissolution test
  - Weight variation
  - Content uniformity test
- Comply with physicochemical properties of gelatin which are a function of parent collagen, pH value, thermal degradation and electrolyte contents

7.1.3. Formulation

- Powder formulation
- Formulation for filling properties
- Formulation for release of API [drug]
- Formulation for position release

Formulation = Drug + excipients + additives

Capsule excipients are similar to those required for formulation of tablets

These are:

- Diluents
- Binders
- Disintegrants
- Surfactants
- Glidants
- Lubricants
- Dyes or colorants ???

Types of excipient	Uses of excipients
Diluents	Give plug-forming properties
Lubricants	Reduce powder to metal adhesion
Glidants	Improve powder flow
Wetting agents	Improve water penetration
Disintegrant	Produce disruption of powder mass
Stabilizers	Improve product stability

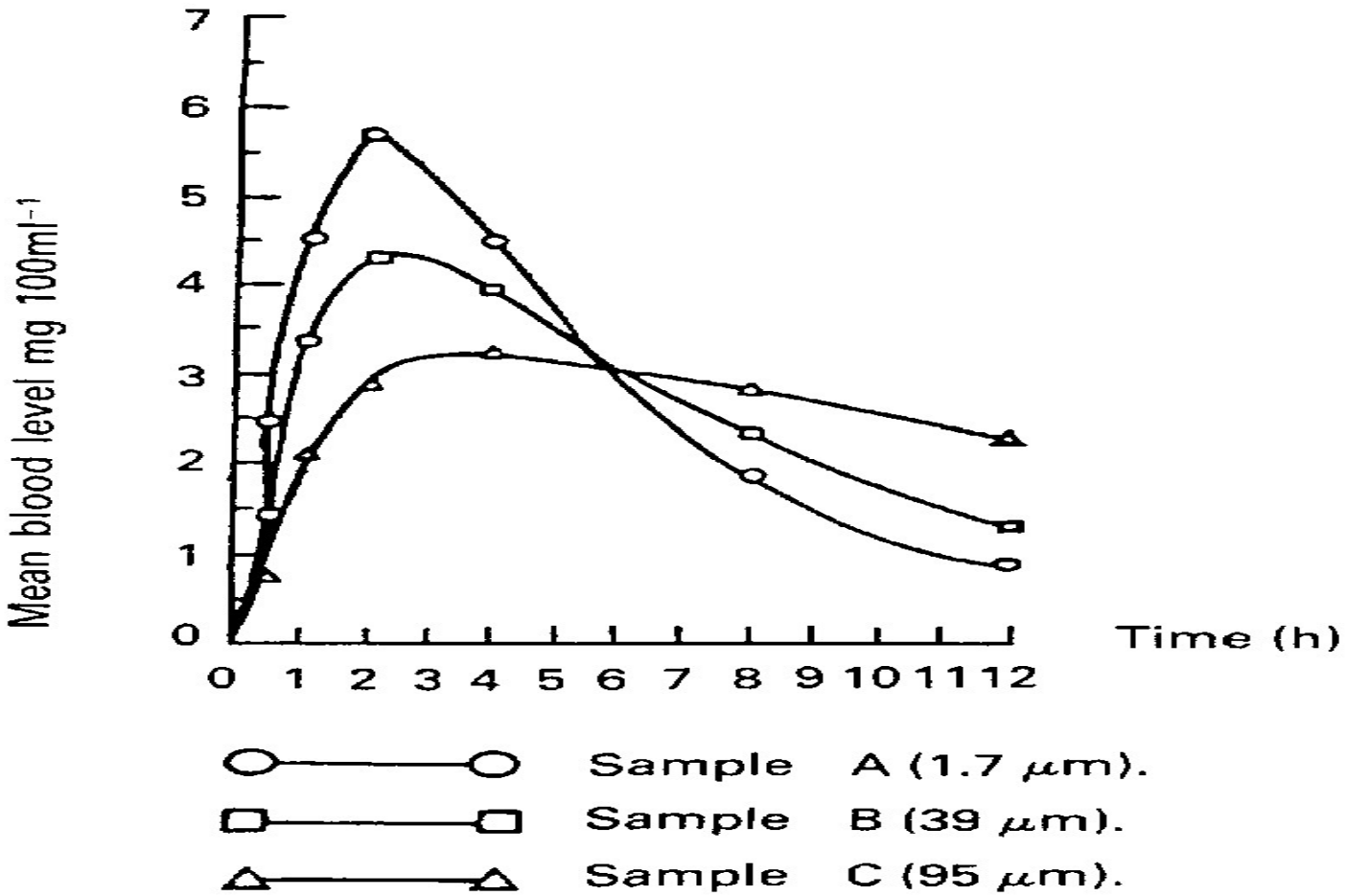
Powder formulation

- Majority of products for filling into capsules are formulated as powders [or Drug + Excipients].

Factors for selection of fill powder:

- Size of capsule to be used
- Properties of active drug
  - ✓ Dose
  - ✓ Solubility
  - ✓ Shape
  - ✓ Particle size

Effect of particle size on bioavailability



Formulation for filling properties

The three main factors in powder formulation:

- Good flow: Use free-flowing diluent & glidant
- No adhesion: Use lubricant if any
- Cohesion (plug-forming diluent) or use flow promoters

Formulation for position release

- Many products are formulated to release their contents in stomach. However, this may not always be the best place for absorption of drug
- Capsule formulation can be readily manipulated to release their contents at various positions along the git
  - ❖Floating capsule coated with hydrophilic polymer such as CMC that swell and float in the stomach
  - ❖Enteric coated capsule
  - ❖Capsule filled with enteric coated pellet
  - ❖Capsule targeting colon-specific enzymes

Formulation optimization

Refers to :

1. Establishing optimal amount of functional excipients [lubricant, disintegrant, binder] that give required disintegration time and dissolution rate
2. **Identifying formulation factors that aid release of active ingredients**

- Active ingredient: Optimum particle size
- Hydrophilic mass : Relating solubility of active to excipients, eg :Superdisintegrant
- Dissolution aids: ,wetting agent,
- Optimum formulation for filling and release

7.1.4. Quality control

Filled capsules are controlled and evaluated for three quality parameters

1. **Weight variation:** Used to confirm weight uniformity
2. **Disintegration test**: Conducted at 37±0.5 °C in disintegration apparatus. The time required for the capsule content to disintegrate and pass via the mesh is called disintegration time[DT]
3. **Dissolution test**: Help to determine capsule content uniformity in a simulated medium at 37±0.5 °C using dissolution apparatus

7.2. Soft gelatin capsules

- Description of the soft gel
- Rationale for selection of soft gel
- Manufacture of the soft gel (formulation & product QC)

Soft gelatin capsules :

- Hermetically sealed one - piece capsules containing a liquid or a semisolid fill
- Like liquid - filled hard capsules, although the drug is presented in a liquid formulation, it is enclosed within a solid, thus combining the attributes

Types of soft gel or soft gelatin capsules

- ❖ Swalowable soft gels: release its content in the stomach
- ❖ Chewable soft gel
  - ➢ Shell is highly flavoured
  - ➢ Drug is incorporated in the shell & fill matrix
  - ➢ Drug is released upon chewing
- ❖ Suckable soft gels : contains flavoured medicament inside its shell
- ❖ Meltable soft gels: used as pessaries or suppository

Advantages of soft gelatin capsules (soft gels)

1. Improved bioavailability, as the drug is presented in a solubilized form
2. Enhanced drug stability
3. Popular for pharmaceuticals, cosmetics & nutritional products
4. Consumer preference regarding ease of swallowing, convenience, & taste can improve compliance
5. Offer opportunities for product differentiation via color, shape, and size
6. Soft gels can be enteric coated for delayed release.
7. Formulations are tamper evident and can be used for highly potent or toxic drugs

Disadvantages of soft gelatin capsules (soft gels)

- Highly water - soluble drugs & aldehydes are not suitable for encapsulation in soft gels.
- Require specialist manufacture
- Incur high production costs

Manufacture of Soft Gelatin Capsules

- The shell is primarily composed of gelatin, plasticizer, and water (30 – 40% wet gel),& the fill can be a solution or suspension, liquid, or semisolid.
- Glycerol is the major plasticizer used, although sorbitol and propylene glycol can also be used. Other excipients are dyes, pigments, preservatives, and flavors
- The glycerol – gelatin solution is heated and pumped onto two chilled drums to form two separate ribbons (usually 0.02 – 0.04 in. thick) which form each half of the softgel.
- Ribbons are lubricated & fed into filling machine, forcing the gelatin to adopt the contours of the die. The fill is manufactured in a separate process and pumped in, and the softgels are sealed by the application of heat and pressure. Once cut from the ribbon, they are tumble - dried and conditioned at 20% relative humidity

- Fill solvents are selected based on a balance between adequate solubility of the drug and physical stability. Water - miscible solvents such as low - molecular – weight PEGs, polysorbates, and small amounts of propylene glycol, ethanol, and glycerin can be used. Water - immiscible solvents include vegetable and aromatic oils, aliphatic, aromatic, and chlorinated hydrocarbons, ethers, esters
- Emulsions, liquids with extremes of pH (< 2.5 and > 7.5), and volatile components can cause problems with stability, and drugs that do not have adequate stability in the solvents can be formulated as suspensions

Unit 8: Pharmaceutical Aerosols

- Introduction
- Components of Aerosol
- Formulation of Pharmaceutical Aerosols
- Stability Testing of Pharmaceutical Aerosols
- Manufacture of Pharmaceutical Aerosols
- Quality control for Pharmaceutical Aerosols

Introduction

Definition

- Aerosols are colloidal dispersions of liquids or solids in gases
- Pharmaceutical aerosol is a system that depends on power of compressed or liquefied gas to expel contents from the container as particles or liquid droplets
- Pharmaceutical aerosol can be available as a solution or suspension
- The terms aerosol, pressure package and pressurized package are interchangeably used

Advantages of Aerosol dosage forms

- ❖Many doses (up to 200) can be filled in the small canister
- ❖MDIs are portable, disposable, have low cost & reproducible dose delivery
- ❖Removal of a dose without contamination of remaining doses
- ❖ Enhance stability of moisture &/ or oxygen sensitive substances due to haermetic seal & inert conditions created by propellant vapour
- ❖Sterility of the sterile products is retained during shelf life & at the time of use
- ❖Medication can be delivered directly to affected area in a desired form such as spray, stream, quick-breaking foam or stable foam
- ❖Irritation produced by mechanical application of topical medication is reduced or eliminated
- ❖Ease of application & application of medication in a thin layer

Disadvantages of Aerosol dosage forms

- Physical stability of pharmaceutical aerosols may be problematic as some aerosol are disperse system
- Ineffective use of drugs as drugs from aerosol may fail to reach proposed site of pharmacological action

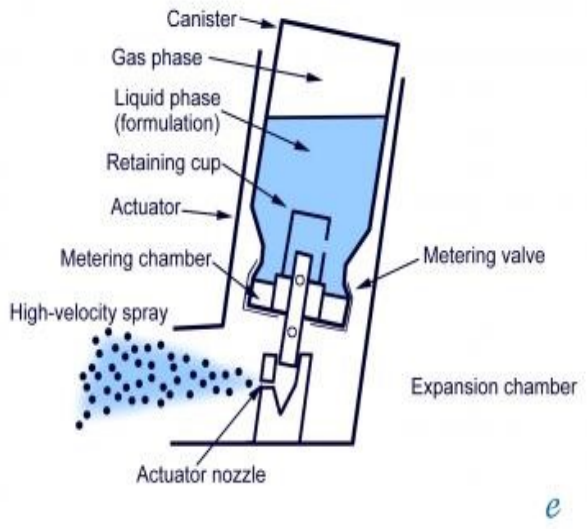
Example

- Deposition of drug in the upper airways[nose, throat, pharynx, larynx] from some dosage forms such as conventional aerosols lowers efficacy of the drug

  Reason: Lack of synchronisation between actuation of dosage form and inhalation
- Presence of high volumes of mucus may impede deposition of drug to lower airways [trachea, bronchi, bronchioles, alveoli]

Components of Aerosol Package

1. Propellant	**3. Valve & Actuator**
2. Container	4. Product concentrate



1. Propellant

- Available as a liquid or compressed gas
- Develops proper pressure within the container
- Expels the product when the valve is opened
- Aids in atomization or foam production of a product

Types of Propellant	Examples of Propellant	Types of aerosol they are used to prepare
Fluorinated hydrocarbons	✓ Trichloromonofluoromethane (propellant 11) ✓ Dichlorodifluoromethane (propellant 12) ✓ Dichlorotetrafluoroethane (propellant 114)	Oral Aerosol and Inhalation aerosol
Hydrocarbons and compressed gases	Propane, Butane, Iso-butane Nitrogen, CO_2 & nitrous oxide	Topical Aerosols

Note:

- Blends of various fluorocarbon propellants are generally used for manufacturing
- Pharmaceutical aerosol formulations generally comprise blends of CFC-11 and CFC-12 or CFC-11, CFC-12 and CFC-114 together with a surfactant such as a sorbitan ester, oleic acid or lecithin, which acts as a suspending agent and lubricates the valve
- Effective propellant pressure is computed as per Raoult's Law.

Raoult's Law

$$Pa = \frac{na}{na + nb} \times PAo = NA \times PAo$$

$$Pb = \frac{nb}{na + nb} \times PBo = NB \times PBo$$

$$P = Pa + Pb$$

Where,

- Pa & Pb are partial pressure of propellant A & B, respectively
- PAo & PBo are Vapor pressure of propellant A & B, respectively
- na & nb are moles of propellant A & B respectively
- NA & NB are mole fraction of propellant A & B, respectively
- P is total vapor pressure of the system
- All pressures are in pounds per square inches absolute [psia]

Examples

1. Calculate the vapor pressure at 20 ^{0}C of a propellant blend consisting of propellant 12/11(30: 70). The vapour pressures of pure propellant A & B are 13.4 & 84.9 psia, respectively

Solution

•Moles of each propellant can be:

•Moles11 = Wt 11/ MW11 = 70/ 137.38 = 0.5095 moles of propellant 11

•Moles12 = Wt 12/ MW12 = 30/ 120.93 = 0.2481 moles of propellant 12

From Raoult's Law:

$P_{11} = [n_{11}/n_{11}+n_{12}]\ p^0_{11}$

$=[0.5095/0.5095+0.2481]13.4=$ 9.01 psia, partial pressure of propellant 11

$P_{12} =[\ n_{12}/n_{11}+n_{12}]\ P^o_{12}$

$=$ 0.2481/ 0.5095+0.2481]84.9 $=$ 27.80 psia, partial pressure of propellant 12

$P= P_{11}+ P_{12} = 9.01 + 27.80 =$ 36.8 Psia , total vapor pressure of the system

2. Calculate the total vapour pressure of a mixture of propellant 11 and propellant 12 which is found at 60:40 ratio in the system and the vapor pressures of propellant 11 & 12 are 89 & 568 kPa, respectively, at 20°C

Solutions

A. Determination of mole &mole fraction of each propellant in the mixture

- Propellant 11 (molecular weight 137.50 g/mol)

  № of moles of propellant 11= n_{11}= 60.00/137.50 = 0.44

- Propellant 12 (molecular weight 121.00 g/mol)

  № of moles of propellant 12= n_{12} = 40.00/121 = 0.33

- Total number of moles of propellants in the system

  $n_{total} = n_{11}+n_{12} = 0.44 + 0.33 = 0.77$

- Mole fraction of propellant 11 & 12

  $X_{11} = n_{11}/n_{11}+n_{12} = 0.44/0.44+0.33 = 0.57$

  $X12 = n_{12}/n_{11}+n_{12} = 0.33/0.44+0.33 = 0.43$

B. Determination of partial vapour pressures of each component in the mixture

- Partial vapour pressure of propellant11

$$P_{11} = X_{11} \times P^{o}_{11} = 0.57 \times 89\text{kPa} = 50.86\ \text{kPa}$$

- Partial vapour pressure of propellant 12

$$P_{12} = X_{12} \times P^{o}_{12} = 0.43 \times 568\ \text{kPa} = 243.43\ \text{kPa}$$

C. Calculation of total vapour pressure within canister

- $P_{total} = p_{11} + p_{12} = 50.86 + 243.43 = 294.29\ \text{kPa}$

2. **Containers** are formed of metal such as [tin plated steel, Aluminum and stainless steel] and glass
3. **Valves** are used to open & close the whole system & capable of controlling delivery of content in predetermined amount

- The three main types of aerosol generating device for use in inhaled drug therapy includes:
  - Metered-dose inhalers
  - Dry powder inhalers
  - Nebulizers

Metered-dose inhalers [MDI]

- The most commonly used inhalation drug delivery devices for treating asthma, chronic obstructive pulmonary disease (COPD) and other respiratory diseases.
- The medication in a metered dose inhaler is most commonly a bronchodilator, corticosteroid &less commonly used mast cell stabilizers, such as cromoglicate or nedocromil.
- In MDIs, drug is dissolved or suspended in a liquid propellant mixture together with other excipients, including surfactants, and presented in a pressurized canister fitted with a metering valve
- A predetermined dose is released as a spray on actuation of the metering valve
- When released from canister the formulation undergoes volume expansion in the passage within the valve and forms a mixture of gas and liquid before discharge from the orifice
- The high speed gas flow helps to break up the liquid into a fine spray of droplets

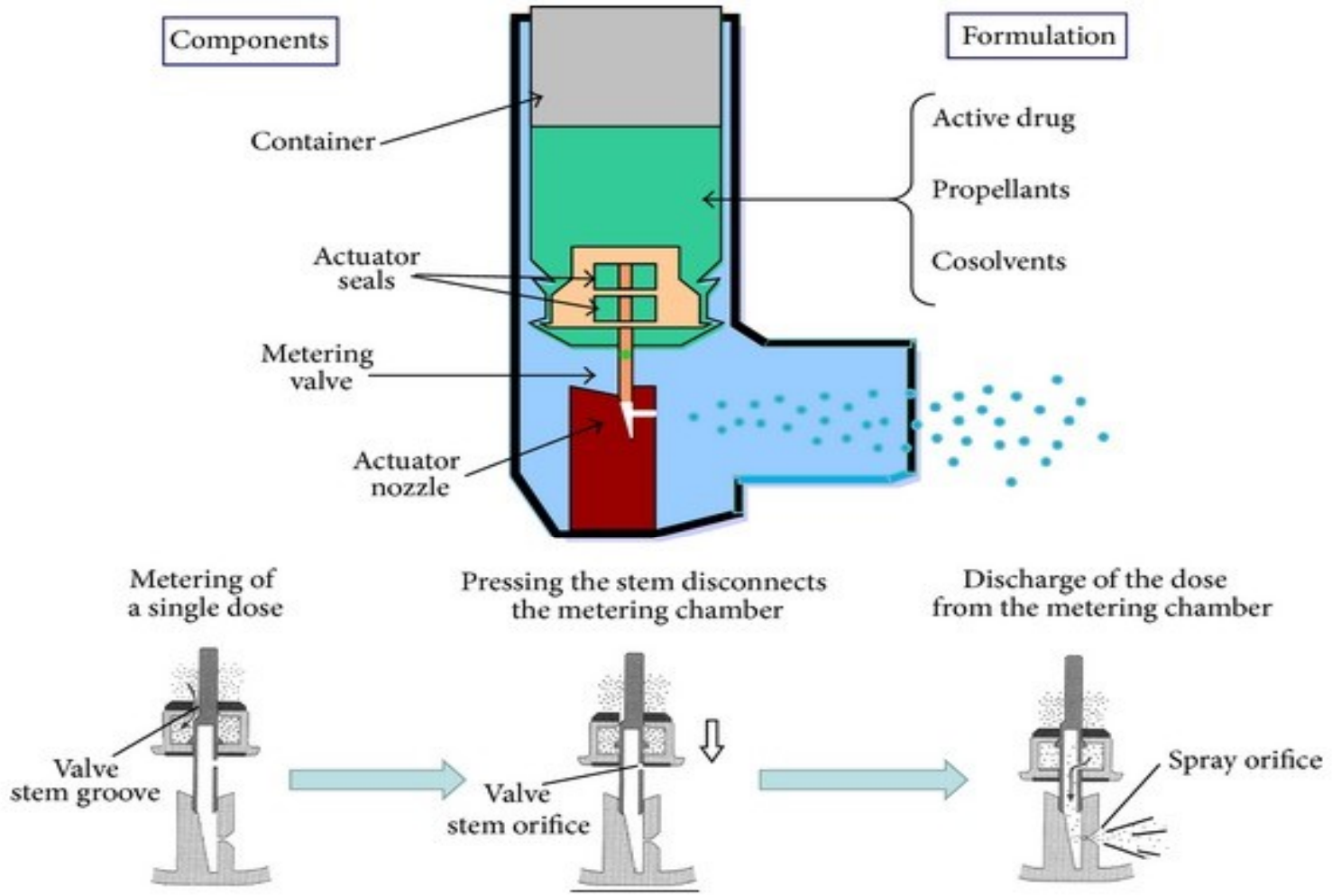
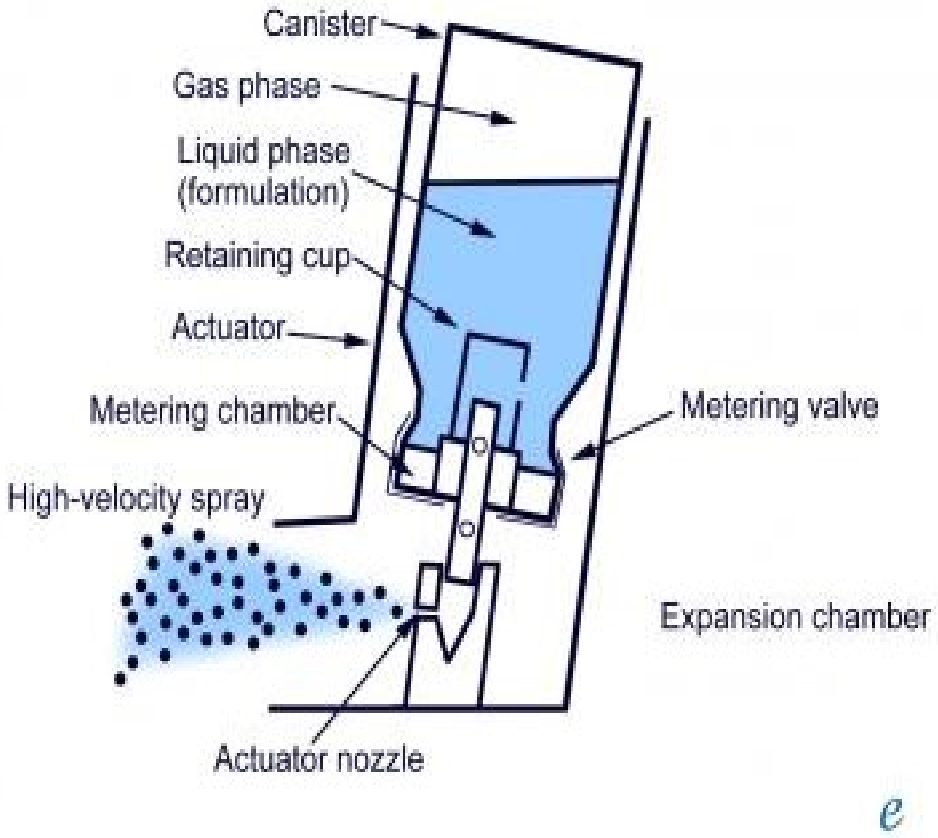
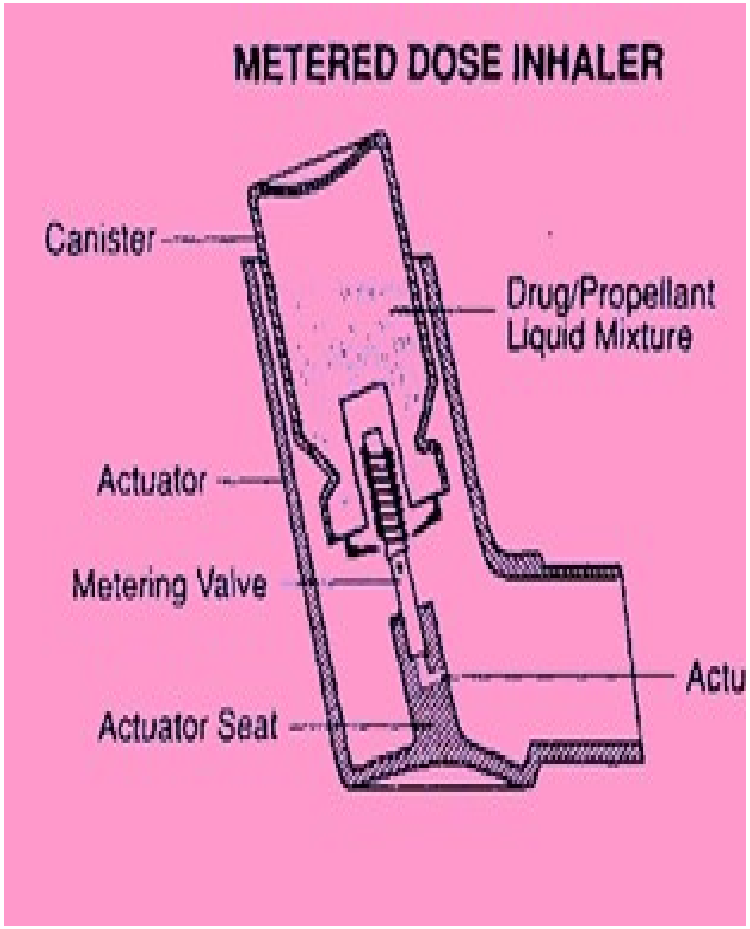


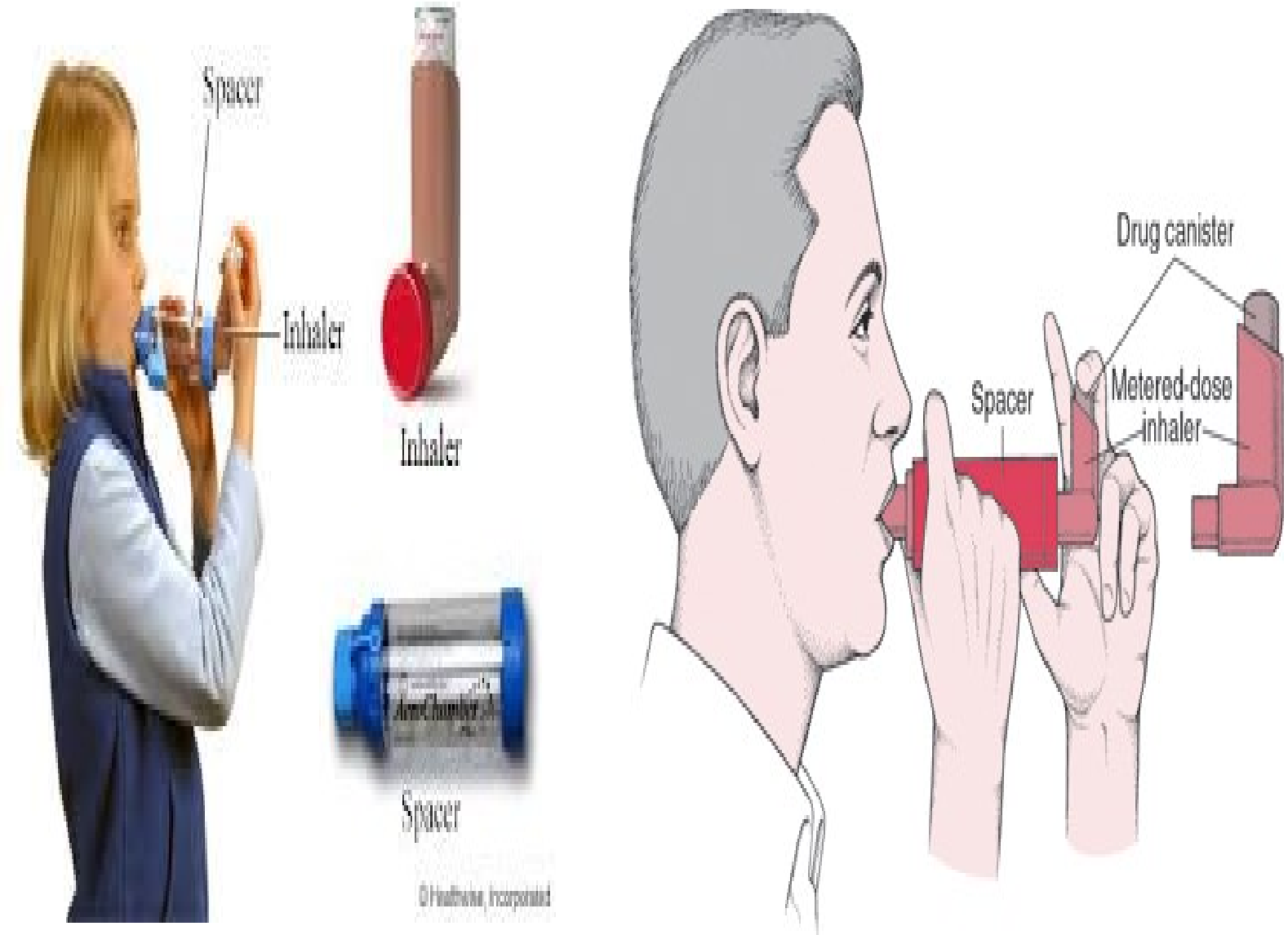
Fig.: The metered-dose inhaler [MDI]


Canister
Gas phase
Liquid phase
(formulation)
Retaining cup
Actuator
Metering chamber
Metering valve
High-velocity spray
Expansion chamber
Actuator nozzle


METERED DOSE INHALER
Canister
Drug/Propellant
Liquid Mixture
Actuator
Metering Valve
Actu
Actuator Seat

Spacer device

- Following actuation the propellant droplets (containing suspended particles of therapeutic agent) will reside within the spacer device, thereby facilitating evaporation of the propellant and allowing the patient to inspire the dose of drug without the need for coordination between actuation of the MDI and inhalation.
- One disadvantage of spacer systems is their size (rendering them conspicuous in use and relatively non-portable)


Spacer
Inhaler
Inhaler
Spacer
© Healthwise, Incorporated
Drug canister
Spacer
Metered-dose inhaler

4. Product concentrate

- Pharmaceutical aerosol formulations generally consists of two components namely propellant & product concentrate
- The product concentrate is composed of the drug (dispersed or dissolved), a surfactants(s), antioxidant, solvent or co-solvent (to enhance drug solubility within the propellant)
- Single or blend of various propellants are used
- Just as a blend of solvents is used to improve drug solubility or mix of various SAA are used to get proper HLB value to formulate stable emulsion system, propellant is selected to give desired vapor pressure, solubility & particle size

- Pharmaceutical aerosol can be dispensed as a fine mist, wet spray, quick-breaking foam, stable foam, semisolid or solid depending on the type of aerosol system utilized
- The type of system selected depends on such factors as physicochemical & pharmacologic properties of active agent and site of application.
    - ❖Solution system
    - ❖Water based system
    - ❖Disperse [Suspension] system
    - ❖Foam systems

- **Solution system** is a two phase system consisting of vapor & liquid phases.
- When the active ingredients are soluble in the propellant, no other solvent is required.
- Depending on the type of spray required, the propellant may consists of propellant 12 or a mixture of propellant 12 & other propellants such as propellant 11 or propellant 114

- **Water- based system** is a three phase aerosol system consisting of propellant, water & vapor phases
- The propellant & water are immiscible
- Ethanol can be used as a cosolvent to solubilize some of the propellant in water. In addition, ethanol is used to produce small particles by virtue of its surface-tension-lowering properties
- SAAs that have low water solubility & high nonpolar solvent solubility are used to produce homogenous disperse systems

Example:

- Long chain fatty esters of polyhydroxylic compounds such as Glycol, glycerol and sorbitol esters of oleic, palmitic, stearic & lauric acids are used

Suspension or dispersion systems involves a dispersion of active agents in a propellant or mixture of propellants. Various SAAs or dispersing agents are used to decrease rate of settling of suspensoids. They are used as oral aerosols. Example

Ingredients	**% weight**
➢Epinephrine bitartarate [1-5µm]……..	0.5
➢Sorbitan trioleate ……..	0.5
➢Propellant 114 ……	49.5
➢Propellant 12……..	49.5

Note: Epinephrine bitartarate has a minimum solubility in propellant system but sufficiently soluble in the fluid in the lungs to exert a therapeutic activity

Approach to increase physical stability of aerosol dispersion includes:

- ❖Moisture content control
- ❖ To use active ingredients having minimum solubility in the propellant system
- ❖Reduction of initial particle size to less than 5µm
- ❖ Adjusting density of propellant &/ or suspensoids so that they are equalized
- ❖Use effective dispersing agents

Dry-powder inhalers [DPIs]

- Powder enters respiratory tract as the patient inhales air through the device
- Powder flow is activated whenever the patient inhales and therefore no fluid propellant is required

DPI formulation = Drug powder + Excipient powders

Note: MDIs are more efficient respiratory delivery systems than their dry-powder comparators

Function of excipients used in DPI formulations

- Facilitate production process by enhancing quality of filling process via increasing fill volume of the mix containing low amount of therapeutic agent
- Improve flow properties of therapeutic agent during inhalation by preventing drug particles aggregation & /or interaction with the plastic interior of the device subsequently, avoids delivery of variable & inaccurate dose to the patient
- Carrier-drug interaction depends on such factors as :
    - surface areas and surface energies of particles
    - morphologies of the particles

Nebulizers

- Nebulisation involves application of high velocity gas or ultrasonic systems to a drug solution to form inhalable solution droplets through a facemask
- The use of a jet or ultrasonic nebuliser is generally reserved for the treatment of acute conditions such as acute asthma, respiratory infection,

Formulation of nebuliser solutions

- Vehicle for sterile nebulizer solutions is water for injections since nebuliser solutions are sterile
- Co-solvents of propylene glycol , glycerol, ethanol can be used in nebuliser solutions to increase solubility of the drug
- Water soluble antioxidants for oxidizable drugs
- Osmolality-modifying agents such as sodium chloride, potassium chloride, mannitol can be used to formulate iso-osmotic nebulisation solutions

Reason: Non iso-osmotic solutions cause bronchoconstriction

Note:

1. pH of nebuliser solutions is kept > 5 using buffers such as citrate, phosphate
2. Generally, nebuliser solutions are packaged as single-dose

Stability Testing of Pharmaceutical Aerosols

- Pharmaceutical Aerosols must be tested for three areas since evidence of decomposition or deterioration in these areas result in having ineffective products

✓ Concentrate & propellant : Product must be tested for vapor pressure, valve spray rate, pH, density, viscosity, total weight, drug assay, odor and color

✓ Container:

- Remove the content after chilling to $\leq 0^0$F., then,
- For metallic container & closure, check for corrosion ,forming small pin holes
- For plastic containers & closures test for leaching, or sorption

✓ Valve: Must be tested for functionality, corrosion, softening, cracking, elongation or distortion

Manufacture of Pharmaceutical Aerosols

- Preparing & packaging of pharmaceutical aerosol demands special knowledge, skills & dedicated equipments
- Addition of propellant to the concentrate is done during packaging operation
- In addition to equipments used to prepare concentrate, special equipments capable of handling & packaging materials at relatively low temperature[-40^{o}F] must be available

Methods to manufactured Aerosols

- Pressure filling
- Cold filling

Pressure filling

- Therapeutic agent and excipients are mixed with a portion of a propellant having relatively high boiling point and low vapour pressure at or below 20°C

Example:Trichloromonofluoromethane(23.7°C& 89 kPa)

- Drug/propellant slurry is then filled into canister and the canister is then crimped with the attached valve
- The second more volatile propellant is then filled into the canister through the valve under pressure until the correct propellant blend is attained

Cold filling

- The drug, excipients and propellants are mixed under cold conditions (circa –30°C)
- The mixture of the formulation is filled into the canister & then the latter is crimped with the attached valve
- Correct mass of the propellant is then added into the canister through the valve at same temperature

Quality Control for pharmaceutical aerosols

- **Propellants** should be tested for vapor pressure, density, identity and purity before used
- **Valves, Actuators & Dip tubes** are subjected to physicochemical inspection for fittings of parts & proper functioning
- **Containers** must be inspected as per standard specifications and checked for weight, spray and leak tests

Testing of pharmaceutical aerosols

- They can be evaluated by a series of physical, chemical & biologic tests mentioned below.
  - Flammability & combustibility
  - Physicochemical characteristics [Vapor pressure, density, Moisture content, Identification of propellant(s), Propellant-concentrate ratio]
  - Performance [Aerosol valve discharge rate, Spray pattern, Dosage with metered valves, Net contents, Foam stability, Particle size determination, Leakage]
  - Biologic characteristics[Therapeutic efficacy & toxicity]

Quiz, May 13/2013EC , Section-B, May 16/2013EC , Section-C

Write true or false & give reasons for each answer

1. Tablet ejection stage is preceded by movements of upper & lower punches in opposite directions
2. Press coated tablets are produced via deposition of coating polymer on conventional tablets
3. Gelatin shell filled with medicated powder consisting of aldehyde reminant definitely passes disintegration test.

Show all computation steps

1. A blend of three propellants known as propellant-A, B & C found at 30:20:50 ratio in the system with respective molecular weight of 210, 120 &250 was used. The vapor pressures of propellant-A ,-B & -C are 90, 120 & 568 kPa, respectively, at 20°C. Calculate optimal vapour pressure expected to be in the canister.

May 16/2013EC , Section-C

Write true or false & give reasons for each answer

1. Tablet ejection stage is preceded by movements of upper & lower punches in opposite directions
2. Press coated tablets are produced via deposition of coating polymer on conventional tablets
3. Gelatin shell filled with medicated powder consisting of aldehyde reminant definitely passes disintegration test.

Show all computation steps

1. A blend of three propellants known as propellant-A, B & C found at 30:20:50 ratio in the system with respective molecular weight of 210, 120 &250 was used. The vapor pressures of propellant-A ,-B & -C are 90, 120 & 568 kPa, respectively, at 20°C. Calculate optimal vapour pressure expected to be in the canister.

May 24/2013EC , Section-A

Write true or false & give reasons for each answer

1. Formulation optimization refers to increasing quantities of each components of the formulation
2. Agieng of shellac is accompanied by prolonging tablet disintegration time
3. Gelatin shell filled with aldehyde based medicated powder passes disintegration test

Show all computation steps

A blend of three propellants known as propellant-A, -B & -C with their respective molecular weight of 120, 210 & 300 was used at 20:24:56 ratio in the system. The vapor pressures of propellant-A ,-B & -C are 568, 90 &120 kPa, respectively, at 20°C.The vapor pressure of propellant-D with mol.weight 350 is about 345 Kpa. What should be the optimal vapour pressure in the canister.

Unit 9: Modified Release Preparations

9.1. Introduction

9.2. Types of modified release preparations

9.3. Mechanisms of drug release

9.4. Kinetics of drug release

9.5. Formulation consideration

9.1. Introduction

- A drug is rarely administered to human being as a pure chemical compound but as a dosage form , a drug product or a drug delivery system suitable for administration
- Almost anything done to dosage form may alter drug availability (rate & amount) to desired place in the body
- For many disease states, the ideal dosage regimen should attain acceptable therapeutic concentration of drug at the site(s) of action immediately following administration and is then maintained constant for the desired duration of therapy

- Administration of right dose size at the right dosage regimen achieves therapeutic 'steady-state' plasma drug concentrations promptly and then maintained by administering repetitive doses of conventional per oral dosage forms
- Administration of medicines by oral route is the most straightforward option for patients. It is the most commonly used route, with more than 70% of all medicines being delivered in this way
- Oral medicines are easy to administer, improve patient compliance and are cheaper than some other alternatives such as injections.

- ‘Conventional per oral dosage form is designed to release rapidly complete dose of drug immediately following administration
- In addition, released drug is assumed to be in a form that is therapeutically active and immediately available for absorption
- Most medicines given by oral route offer ‘immediate-release’ or ‘conventional’ drug delivery to reveal rapid onset of action
- However, some situations need slow drug release profile & long lasting effects which in turn needs modification of drug release pattern

Limitations of ‘Conventional' peroral oral dosage form

1. Drug concentration in plasma & at the site(s) of action fluctuates over successive dosing intervals, even after achieving steady-state' condition. Hence it is not possible to maintain a therapeutic concentration of drug that remains constant at the site(s) of action for the duration of treatment. At best, the mean value of max. & min. plasma conc. associated with each successive dose remains constant for the period of drug treatment

2. Inevitable fluctuations of steady-state concentrations of drug in plasma, and hence at the site(s) of action leads to a patient being over- or under-medicated for periods of time
3. Drugs having short biological half-lives require frequent dosing to maintain steady state plasma concentrations within therapeutic range. For such drugs the maintenance of therapeutic plasma concentrations is particularly susceptible to consequence of forgotten doses & overnight no-dose period
4. Therapeutic inefficiency or failure due to lack of patient compliance is associated with regimens requiring frequent administration of conventional dosage forms

Thus, modified release dosage forms are required.

What are modified release dosage forms?

- They are drug products designed to alter the time & rate of release of bioactive agent (drug substance)
- They refer to manipulation or modification of drug release from a dosage form (e.g. tablet, pellet, capsule) with the aim of delivering active pharmaceutical ingredients (API) at desired rates, pre-defined time points, or specific sites in the git
- They are per oral dosage forms that continuously release drugs at controlled rates to provide periods of prolonged therapeutic action following single dose administration
- They achieve certain therapeutic or convenience objectives that conventional dosage forms never offer

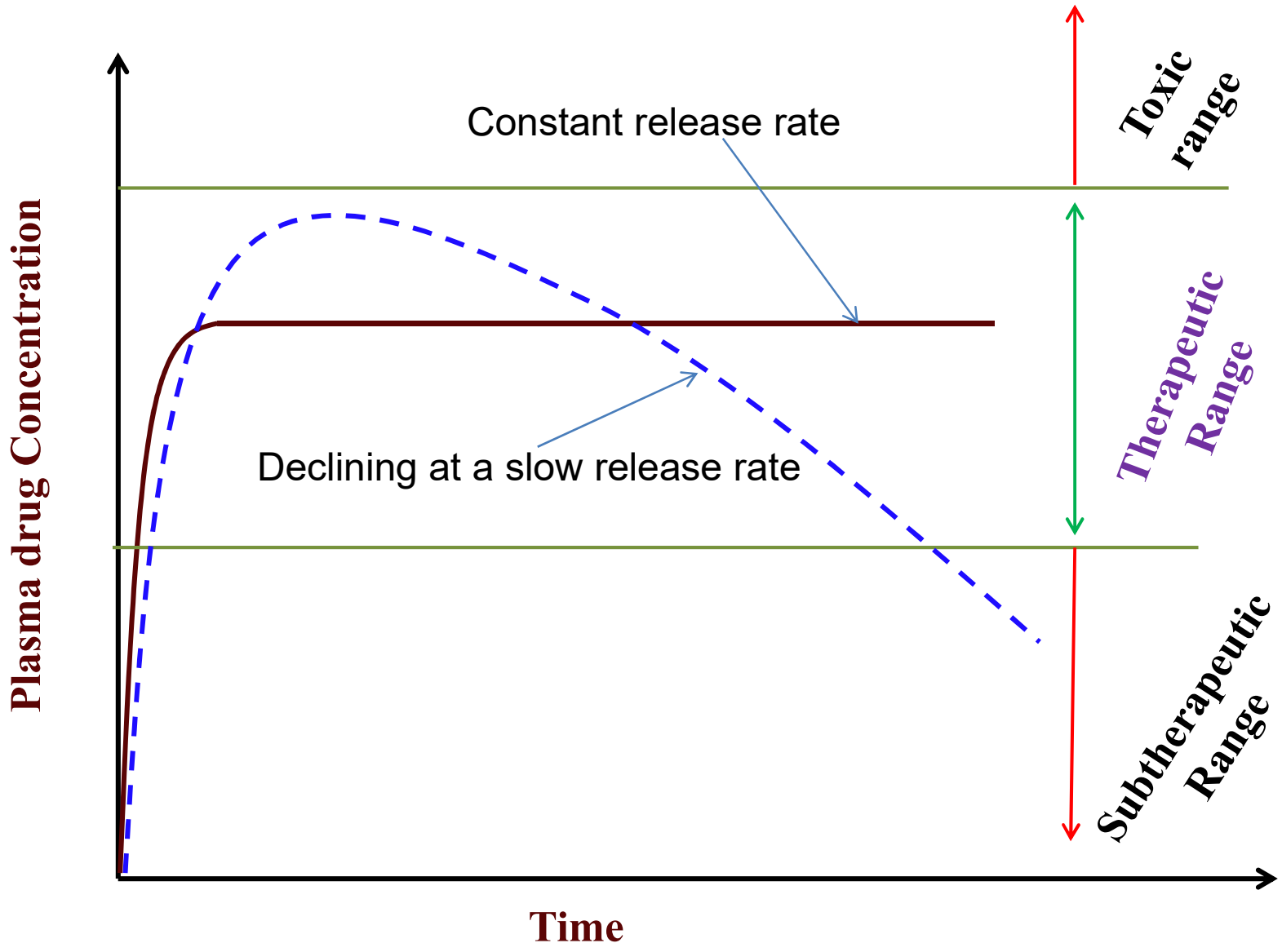
Objectives of modified release dosage forms

Providing either prompt achievement of drug plasma concentration that:

- remains essentially constant at a value within therapeutic range of drug for a satisfactorily prolonged period of time

or

- although not remaining constant, declines at such a slow rate that the plasma concentration remains within the therapeutic range for a satisfactorily prolonged period of time



Serum drug conc. vs. time curves of modified release peroral dosage forms

9.2: Types of modified release dosage forms

A. Delayed release dosage forms
B. Controlled [Prolonged /Extended] release dosage forms
C. Sustained release dosage forms
D. Targeted dosage forms

A. Delayed release or Gastro-resistant dosage forms

Repetitive, intermittent dosing of drug occur from one or more immediate-release units added into a single dosage form

Types of delayed-release dosage forms

1. Repeat-action (release of two doses successively)
2. Enteric coated tablets/capsules : Timed release is achieved by a polymer barrier coating to release drug in the small intestine
3. Modified enteric coated tablets : Additional drug is applied over enteric coat and is released in the stomach, while the enteric coated remainder is released further down the small intestine

B. Controlled (Prolonged or Extended) release d.f

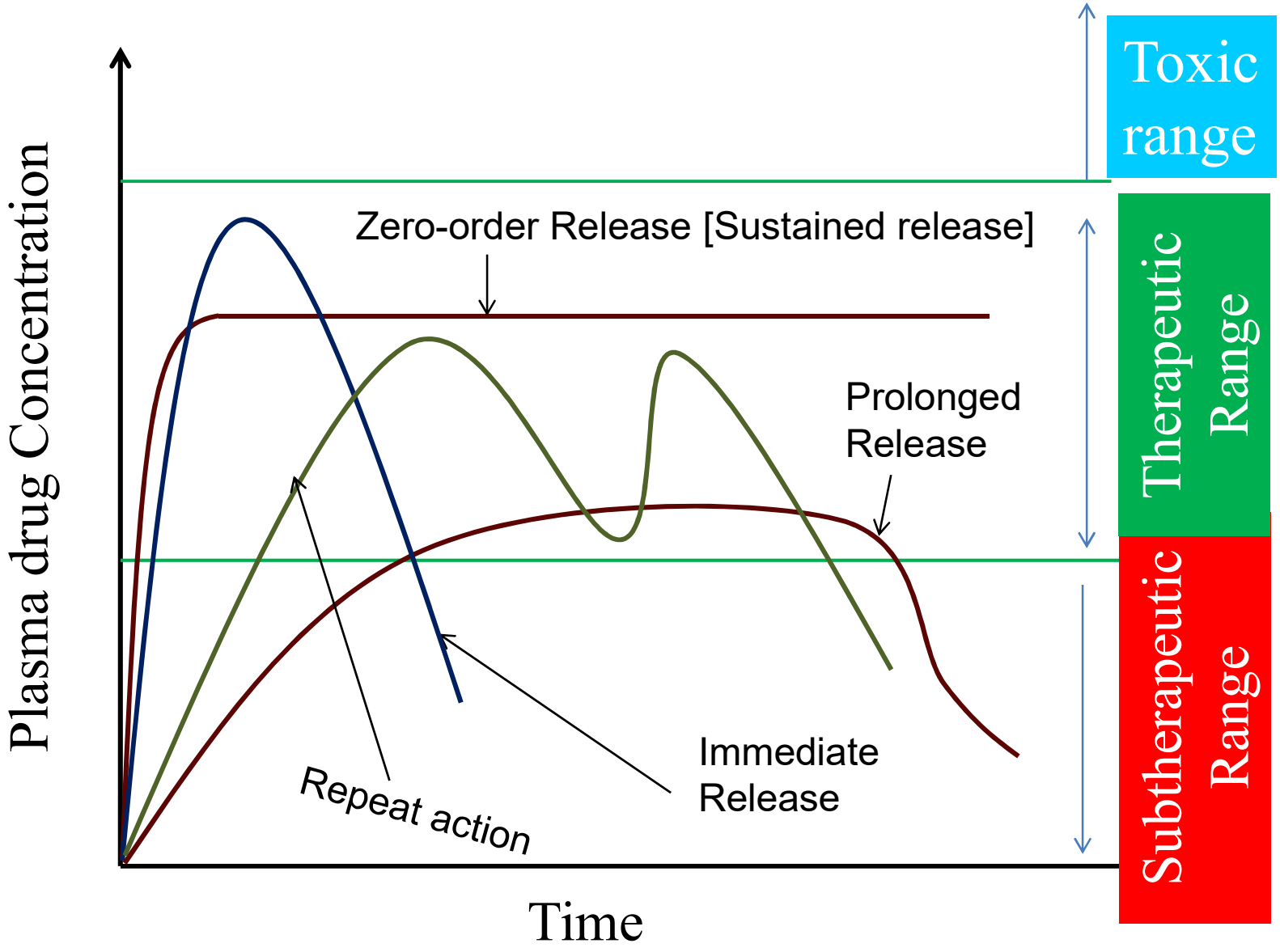
Release drug slowly to maintain constant plasma drug concentration over prolonged duration of therapy, but onset of action is delayed

1. Releases bioactive agent (drug) over extended period of time
2. Avoids undesirable saw tooth features of plasma conc. vs. time profiles of conventional drug products
3. Dosage form controls release rate of incorporated drugs & maintaining constant drug concentrations at the biophase: target tissue or cells, i.e, drug release rate is determined by design of the system & physicochemical properties of drug

4. Drug release rate is independent of external factors [microenvironment] where dosage form is placed
5. Design of controlled release dosage forms is based on the philosophy that when level & time of availability of the drug to the target tissue are optimized, optimum biological response occurs
6. Since release-rate control complements drug molecular structure in determining both selectivity and duration of action, it is believed that controlled-release drug-delivery systems permit more accurate, effective, reproducible & predictable drug administration

C. Sustained release dosage forms

Characterized by initial release of drug sufficient to provide a therapeutic dose soon after administration, and then a gradual release over an extended period



Serum drug concentration vs. time curves of various oral dosage forms

Differences b/n repeat-action & sustained/controlled release preparations

1. Repeat-action product does not release drug in a slow controlled manner, hence never give a plasma concentration-time curve resembling that of a sustained-release product
2. A repeat-action tablet usually contains two or three doses of drug, the first being released immediately to provide a rapid onset of action
3. Release of enteric coated second dose is delayed, until breached by intestinal fluids
4. AUC obtained from repeat-action preparation exhibits 'peak & valley' profile similar to intermittently administered conventional dosage forms

D. Targeted dosage forms

- Two types of targeted dosage forms are commonly described:
  - ➢Site specific targeting
  - ➢ Receptor targeting
- In site-specific targeting, drug release is at diseased organ or site of absorption
- In receptor targeting, drug release is at the receptor for the drug action

Note

- All dosage forms described above can be grouped under the generalized term Controlled Drug Delivery
- CDD is now a generalized term that encompasses any system that is capable of spatial placement and temporal delivery of a drug
- In spatial placement, the drug is targeted to a specific organ or tissue (this includes targeted dosage forms)
- In temporal delivery, the rate of drug delivery to the target tissue is controlled (eg.: delayed and controlled release dosage forms plus pulsatile or modulated drug delivery systems because the rate of delivery is controlled based on human physiological need)

Advantages of controlled release drug delivery systems

1. Increase efficacy by maintaining constant plasma drug level in the therapeutic window range for an extended period of time
2. Reduce dosing frequency
3. Eliminate drug accumulation in the body, thereby minimizing untoward effects
4. Increases patient compliance
5. Minimizes cost of treatment for chronic diseases

Drawbacks of controlled release dosage forms

- Should patient suffer from adverse drug reaction or become accidentally intoxicated, removal of drug from the system may be difficult, if not impossible
- When orally administered it may yield erratic or variable drug absorption owing to interactions with contents of git and changes in gastrointestinal motility resulting in drug ineffectiveness
- Dose dumping from failure of controlled release dosage forms resulting in potentially adverse plasma drug levels

Note

- Dose dumping refers to release of more than the usual fraction of drug or release of drug at a greater rate than the customary amount of drug per dosing interval
- CRD forms are particularly prone to dose dumping if not properly designed and fabricated because they usually contain the equivalent of two or more drug doses present in a conventional dosage form

  For example delayed and enteric coated dosage forms: If poorly formulated, the enteric coating may be dissolved in the stomach, resulting in premature release of drug with the concomitant irritation of gastric mucosa
- Moreover, if the coating is poorly done, the enteric coating may not dissolve at the proper site along the gastrointestinal tract. Thus, the drug may not be available for absorption.

9.3. Mechanisms of drug release

Two basic mechanisms controlling drug release are:

- ❖ Dissolution of the active drug component
- ❖ Diffusion of dissolved or solubilized drug molecules

Four independently, simultaneously or consecutively operating processes are involved within the context of aforementioned mechanisms:

1. Hydrating of the device (swelling of hydrocolloid or dissolution of channelling agent)
2. Diffusion of water into the device
3. Dissolution of the drug
4. Diffusion of dissolved drug out of the device

9.4. Kinetics of drug release for ideal Modified Release [MR] per oral dosage form

- MR per oral dosage form consists of two portions
  - ❖Initial priming/loading dose, Ld
  - ❖ Sustained dose or Maintenance dose, Md.

- Drug Ld is released rapidly into gastrointestinal fluids immediately following administration of MR d.f.
- Released dose is absorbed into body compartment rapidly following a first-order kinetic process i.e. characterized by apparent absorption rate constant, K_a

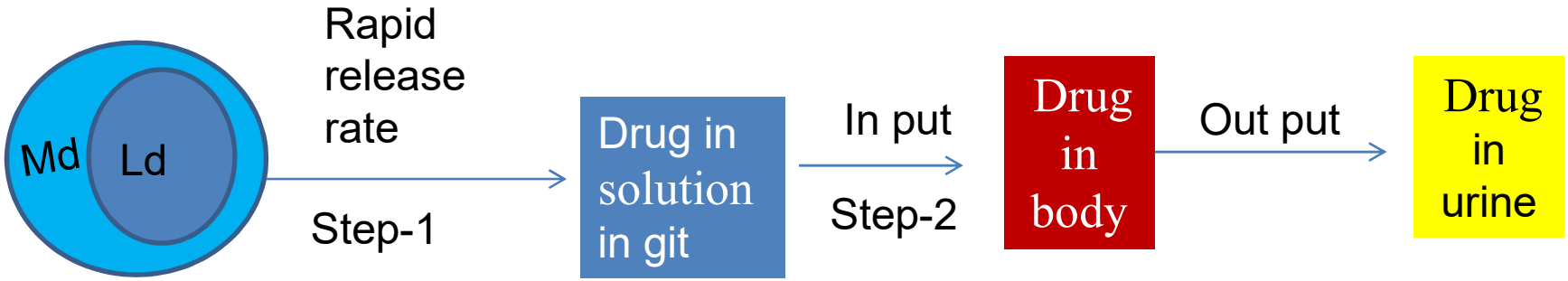
Objective of Ld: Rapid attainment of therapeutic plasma drug conc. that provides rapid onset of action

- The portion Md. of drug remaining in the dosage form is released by zero-order kinetics, i.e. zero-order rate constant, k_o.

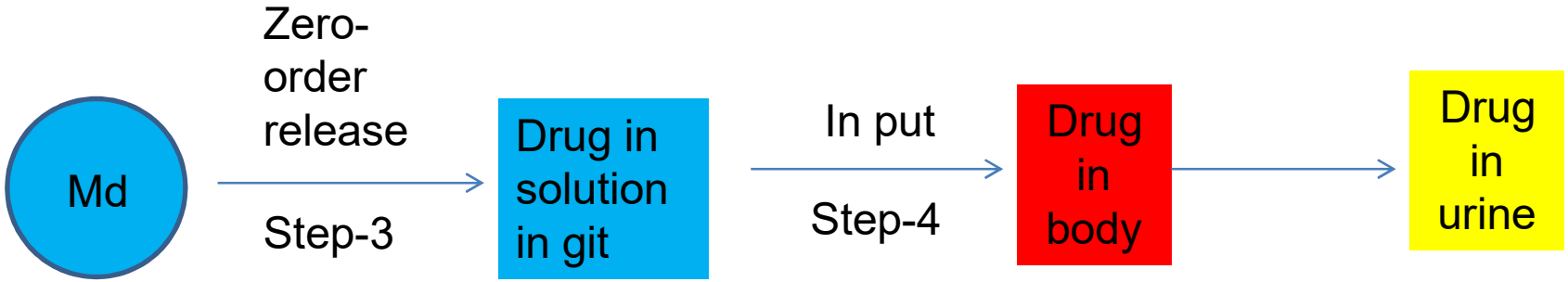
Thus, the rate of release of drug from maintenance dose remain constant independent of amount of drug remaining in the dosage form at any given time

Schematic presentation on kinetics of drug release from MR

A. Release & absorption of initial priming dose [Ld]



B. Release & absorption of maintenance dose [Md]



Conditions that must be fulfilled to ensure therapeutic concentration of drug in the body remains constant

1. MR dosage form must have loading and maintenance doses
2. Drug from Ld must be immediately released and hence absorbed by first order absorption rate constant
3. Zero-order release rate of drug from the Md must be rate determining wrt. the rate at which released drug is subsequently absorbed into the body. Kinetics of absorption of the Md will thus be characterized by the same zero-order release rate constant, k_o
4. The rate at which Md is released from dosage form, & hence the rate of absorption (input) of drug into the body, must be equal to the rate of drug output from the body when the conc. of drug in the body is at the required therapeutic value

9.5. Formulation consideration

Main types of oral modified release delivery systems based on :

A. pattern of drug release

- Monolithic or matrix systems
- Reservoir or membrane-controlled systems
- Osmotic pump systems

B. nature of excipients used

- Inert delivery systems
- Lipophilic delivery systems
- Hydrophilic delivery systems

Types of excipients	Examples of excipients	Types of delivery systems
Inert excipients	Dibasic calcium phosphate Ethyl cellulose Methacrylate copolymer Polyamide Polyethylene Polyvinyl acetate	**Inert delivery system**
Lipid excipients [Lipophilic excipients]	Carnauba wax Cetyl alcohol Hydrogenated vegetable oils Microcrystalline waxes Mono- and triglycerides	**Lipid delivery system [Lipophilic delivery system]**
Hydrophilic excipients	PEG monostearate PEG Alginates Carbopol Gelatin Hydroxypropylcellulose HPMC Methylcellulose	**Hydrophilic delivery system**

Note:

Basic principles governing all aforementioned systems

1. Osmosis occurs from surrounding body fluids into delivery system following water concentration gradient
2. Drug in a solution form diffuses out from the delivery system into surrounding body fluid following drug concentration gradient

Components of a modified-release delivery system

1. Active drug
2. Release-controlling agents [matrix & membrane formers]
3. Matrix or membrane modifier[channelling agents for wax matrices and solubilizers & wicking agents for hydrophilic matrices]
4. Solubilizers, pH &/or density modifiers
5. Lubricant and flow aid [magnesium stearate, stearic acid, hydrogenated vegetable oil, sodium stearyl ,talc, colloidal silicon dioxide]
6. Supplementary coatings to extend lag time, further reduce drug release

Monolithic matrix delivery systems [2 types]

1. Hydrophilic colloid matrices

- Made of drug particles dispersed in a soluble matrix, such that drug is released as the matrix dissolves or swells and dissolves
- Slow dissolution of the matrix provides sustained release pattern of drugs dispersed in a soluble matrix
- Excipients used to provide a soluble matrix often are those used to make soluble film coatings ! HPMC
- Alternatively, slowly dissolving fats and waxes can be used

2. Lipid matrices & insoluble polymer matrices DS

- The drug particles dispersed in an insoluble matrix, is released as solvent enters the matrix and dissolves the drug particles. **How?**
- Drug release from insoluble matrices follows penetration of fluid, followed by dissolution of the drug particles and diffusion through fluid filled pores This type of delivery system is unsuitable for insoluble or poorly aqueous soluble drug
- Excipients used in the preparation of insoluble matrices include hydrophobic polymers, such as polyvinyl acetate, ethylcellulose and some waxes

Reservoir or membrane-controlled drug systems

- Drug release rate is controlled by insoluble but permeable polymeric membrane
- A drug reservoir consisting of drug that should not diffuse in the solid state , e.g. a tablet or multi-particulate pellet, is coated with a membrane
- Aqueous medium such as GI- fluid diffusing into the system and forming a continuous phase through the membrane initiates drug diffusion and release

Components of a membrane-controlled system

A. Core

- ❖ Active drug
- ❖ Filler or substrate [lactose, microcrystalline cellulose, dextrose, sucrose and polyols (mannitol, sorbitol]
- ❖ Solubilizer such as buffers, surfactants,polyols & PEGs
- ❖ Lubricant/glidant such as magnesium or calcium stearate

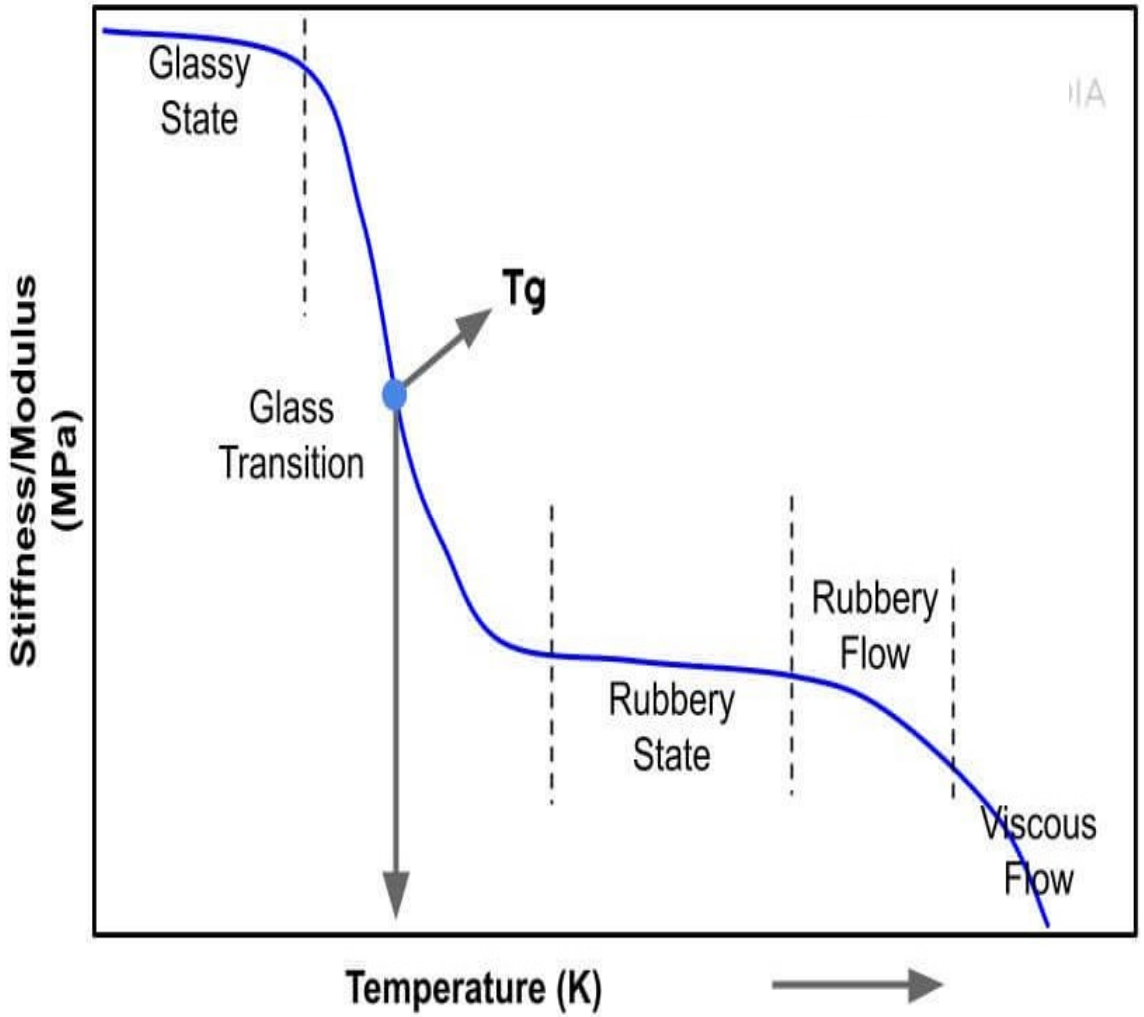
B. Coating

- ➢ Membrane polymer
- ➢ Plasticizer
- ➢ Membrane modifier or channelling agent such as sodium chloride, sugars and Polyols
- ➢ Colour/opacifier

Membrane polymers

- Critical part of the formulation as it controls drug release
- Nature of polymeric material governs drug release rate from reservoir devices.
- It should remain intact for the period of drug release, i.e. without swelling or subsequent erosion, as seen in hydrophilic matrices
- Typical polymers used include **ethyl cellulose**, **acrylic copolymers**
- Polymer with high glass transition temperature & high degree of crystallinity have slow drug release rate

- **The glass transition temperature** is the temperature range where the polymer substrate changes from a rigid glassy material to a soft (not melted) material, and is usually measured in terms of stiffness, or modulus
- Glass transition temperature is the temperature, below which the physical properties of plastics change to those of a glassy or crystalline state. Above T_g they behave like rubbery materials. Below the T_g a plastic's molecules have relatively little mobility



Tg is directly proportional to polymer's :

- **Molecular weight**
- **Cross-linking level**
- **Rigidity**
- **Intermolecular force**

Graph of glass transition temperature plotting temperature versus stiffness of a material

Methods to circumvent very low permeability of the coating polymer

1. Incorporating pore formers or water-soluble additives into the polymer coating

- In the gastrointestinal fluid, the pore-formers in the polymer coating dissolve making porous coating polymer through which lipophilic and hydrophilic drugs can easily diffuse out
- Drug release rate is a function of the total concentration of (both dissociated & undissociated) drug within the core

According to Van't Hoff rule, $\pi = iCRT$, where i, C, R, T are № of molecules /ions, Conc. of solute, gas constant & absolute temperature, respectively

2. **Incorporation of plasticizers** into coating polymer

- They lower glass-transition temperature [Tg] or increase uptake of fluids into the polymer coating
- Based on their solubility level, they may remain in the coating or be eluted to form micro/macr-pores

3. **Employing copolymers** that lower Tg & improve uptake of aqueous fluid since their permeability is adequate without incorporation of any additives

   Example: Tg of such copolymers as methyl methacrylate & ethacrylate is about 5 ^{o}C; hence absorb substantially more water at 37^{o}C than do homopolymers such as polymethylmethacrylate

Note

- In reservoir system, the polymer membrane is only at the surface of the system, whereas in the matrix system, the polymer is throughout the whole system
- In both cases hydration of the polymer is the step that allows the drug to diffuse
- Unlike hydrophilic matrix systems, membrane polymer neither swell on hydration to form a hydrocolloid matrix nor erode
- With the classic membrane system there are two diffusion processes: 'water in' followed by 'drug out'.

Osmotic pump systems[OPS]

- The tablet core consists of osmotically active drug or excipient
- The tablet core that is coated with a semipermeable membrane allows water ingress into the core, to dissolve or suspend the loaded drug
- As the core dissolves/suspends, a hydrostatic pressure builds up and forces (pumps) drug solution (or suspension) through a hole drilled in the coating
- Drug release rate from OPS is governed by the rate at which water ingresses via the membrane, and how quickly the drug solution (or suspension) passes out of the hole

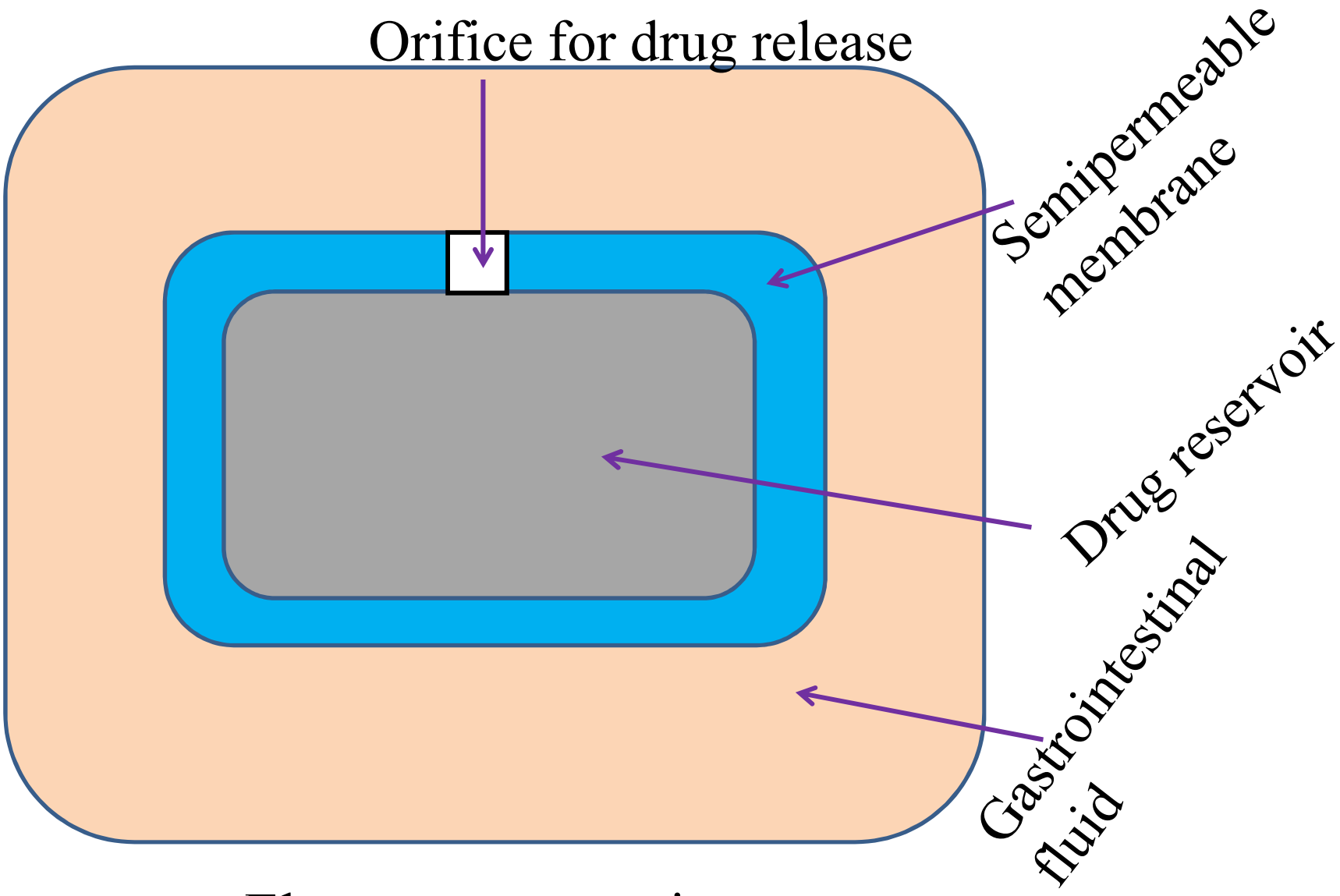
Components of osmotic pump systems

A. Core

- Consists of active drug, a filler or substrate, a viscosity modifier, solubilizer) and lubricant/glidant.

B. Coating

- Coatings contain a membrane polymer, a plasticizer, a (membrane modifier) and (colour/ opacifier).



Elementary osmotic pump

Essential difference between osmotic pump and 'classic' membrane-controlled system

- For osmotic pump only one diffusion process is required ('water in').
- For 'classic' membrane-controlled system two processes are key: water in, drug out

Quiz: Write True /False for the following questions

1. Drug is released from modified dosage forms at constant rate
2. Modified enteric coated dosage forms release drug only in the SI
3. Drug hydrolysis can be minimized by using buffer
4. Escalated temperature prolongs drug shelf-life
5. Osmotic pump system release drug at variable rate
6. Pharmacokinetics of most drugs at their therapeutic doses is governed by both first & zero-order kinetics
7. Drug release from both reservoir & matrix systems involve membrane dissolution
8. $T_{10\%}$ of drug product with order rate constant 0.035 yr^{-} is 3 years
9. The short coming of both extended & sustained release modified preparations is delayed onset of actions
10. Pure drug substance can be used for therapeutic purpose since it has fast dissolution & absorption rate

1. Pharmacokinetics of most drug therapeutic dose is governed by both first & zero-order kinetics
2. Drug release from both reservoir & matrix systems involve membrane dissolution
3. Shelf-life of a drug product is 3 years if its order rate constant at 298K^{o} is 0.035 yr^{-}
4. The short coming of both extended & sustained release modified preparations is delayed onset of actions
5. Pure drug substance can be used for therapeutic purpose since it has fast dissolution & absorption rate

Unit 10: Sterile products

1. Parentral products
2. Types of parentral
3. Product development, vehicles, solutes, containers
4. Production design facilities, steps in processing, packaging
5. Aseptic room & processing, quality control and quality assurance
6. Ophthalmic and other sterile preparations

Unique Properties of Parentral products

- All products must be sterile
- All products must be free from pyrogenic (endotoxin) contamination
- Injectable solutions and reconstituted sterile powders must be free from visible particulate matter
- Products should be isotonic with body fluids
- All products must be chemically, physically and microbiologically (i.e., sterility, freedom from pyrogenic and visible particulate matter) stable
- Products must be compatible with delivery systems, IV diluents,, and other co-administered drug products

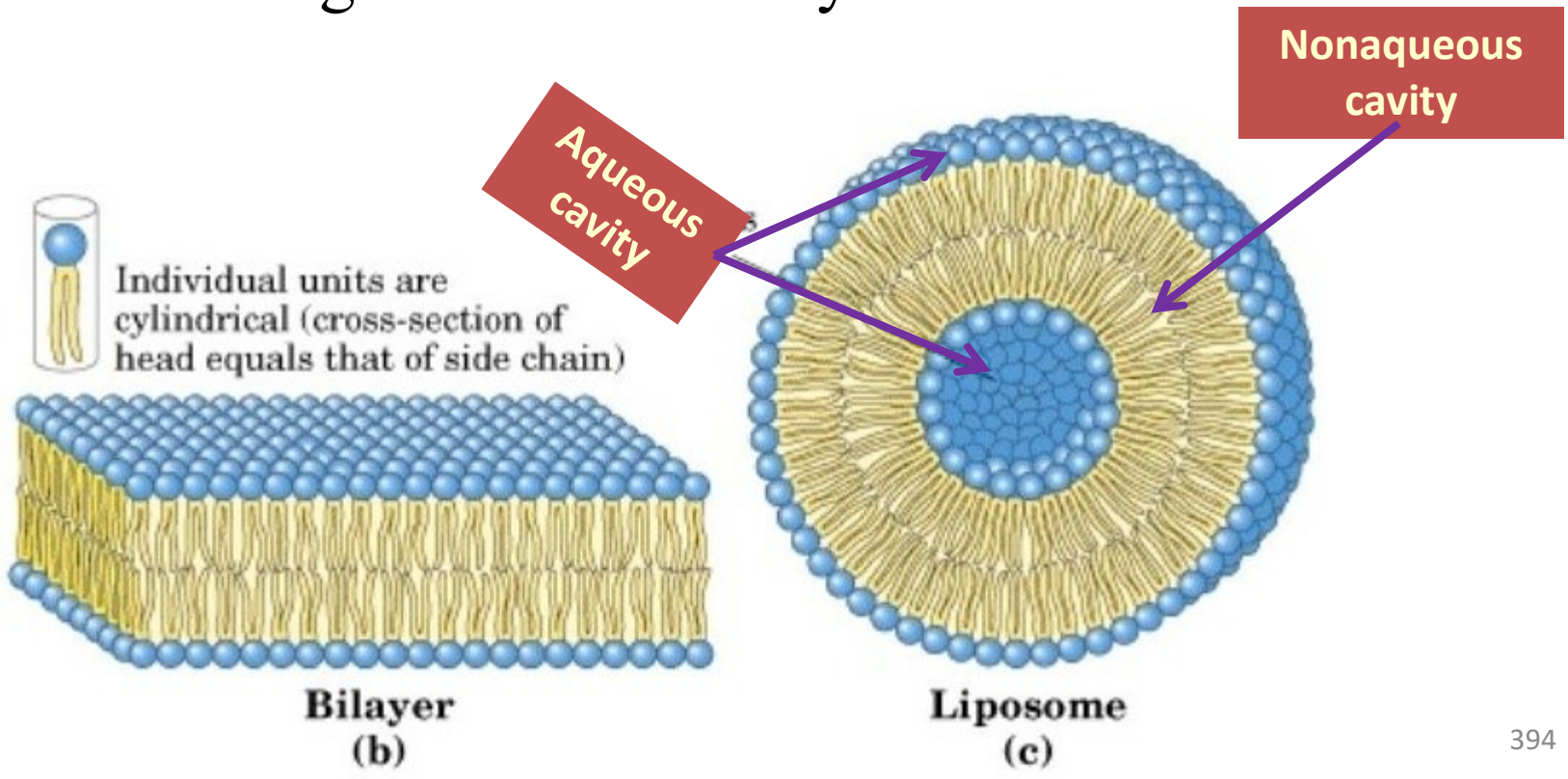
Types of parentral

Parenteral drugs are formulated as:

- Solutions
- Suspensions
- Emulsions
- Injectable powders for reconstitution
- Liposomes
- Microspheres
- Nanosystems

Liposomes

- Formed by self - assembly of phospholipid molecules in an aqueous environment
- Closed sphere may encapsulate aqueous soluble drugs within the central aqueous compartment or lipid - soluble drugs within the bilayer membrane



Attractive Biological Properties of Liposomes

- Biocompatible
- Entrap hydrophilic bioactive compounds in their central aqueous compartment & hydrophobic ones into lipid bilayer membrane
- Liposome incorporated bioactives are protected from inactivating effect of external conditions yet do not cause undesirable side reactions
- Liposomes provide a unique opportunity to deliver pharmaceuticals into cells or even inside individual cellular compartments

Product development: vehicles, solutes, containers

- Development of optimal parenteral formulation requires consideration of formulation components and packaging.

Vehicles

- Component present in the highest proportion since most liquid injections are quite dilute
- The vehicle of greatest importance for parenteral products is water for injection[WFI]; prepared by steam distillation or reverse osmosis.
- WFI is suitable for compounding of parentrals and rinsing of primary packaging for parentrals

Water-Miscible Vehicles

- A number of solvents that are miscible with water have been used as a portion of the vehicle in the formulation of parentral

Uses

- to solubilise certain drugs in aqueous vehicle
- to reduce hydrolysis

The most important solvents in this group are:

- Ethyl alcohol
- Liquid PEG
- Propylene glycol

Non-Aqueous Vehicles

- The most important group of non-aqueous vehicles are fixed oils of vegetable origin such as corn oil, cottonseed oil, peanut oil, and sesame oil

Reason:

- ❖ They will be metabolize after administration
- ❖ They are liquid at room temperature
- ❖ They do not become rancid readily

- Fixed oils are used as vehicles for preparations of certain vitamins (Vitamin K, Vitamin E) & hormones (progesterone, deoxycorticicosterone ,testosterone,)

Solutes

- Parentral grade solutes should be used
- Low microbial level will enhance effectiveness of aseptic or terminal sterilization
- Likewise, nonpyrogenic ingredients enhance the nonpyrogenicity of the finished injectable product.
- Active pharmaceutical ingredients and most excipients must meet microbial and endotoxin limits
- No chemical impurities including trace residues find in parentral grade drug & excipient, since impurities are not removed by product processing

Added Substances or Additives

Uses

- Increase and maintain drug solubility [complexing agents[cyclodextrins] and SAA[Tween 20 and Tween 80]. Solubilizing agents
- Provide patient comfort by reducing pain and tissue irritation via tonicity adjustment [Eg: sodium chloride, dextrose, and glycerin].
- Enhance chemical stability of a solution [antioxidants, inert gases, chelating agents, and buffers].....Stabilizers
- Enhance physical stability of proteins by minimizing self-aggregation or interfacial induced aggregation [SAA] ....Stabilizers

Containers and closures

- They are in prolonged, intimate contact with product and may release substances into, or remove ingredients from, the product
- Rubber closures must be properly evaluated for compatibility problems such as sorption, leaching and permeation]
- Containers & closures should ensure that product retains its purity, potency, and quality throughout its shelf life
- Administration devices such as syringes, tubing, transfer sets should have same quality with containers & closures

Types of containers & closures for injectable formulation

- Container systems : Ampoules, vials, syringes, cartridges, bottles, and bags
- Ampoules are all glass, whereas bags are all plastic
- Other containers can be composed of glass or plastic and must include rubber materials, such as rubber stoppers for vials and bottles & rubber plungers and rubber seals for syringes and cartridges.
- Irrigation solutions are packaged in glass bottles with aluminium screw caps

Production facilities

- Production facility and its associated equipment must be designed, constructed and operated properly for the manufacture of safe and effective sterile product
- Construction materials for sterile product production facilities must be smooth, cleanable and impervious to moisture and other damage

Equipments: Must be constructed from stainless steel materials & never be reactive, additive or absorptive

Functional injectable production areas include:

1. Warehousing or procurement
2. Compounding (formulation)
3. Materials (containers, closures, equipment)
4. Preparation, filtration & sterile receiving
5. Aseptic filling & stoppering
6. Sterilization room for thermostable products
7. Packaging & labeling
8. Quarantine

Extra requirements for the aseptic area

- Equipped with HEPA filter & Laminar Air flow[LAF]
- LAF prevents contamination of products during aseptic filling into individual container
- Design of aseptic area must prevent products from such contaminants as dust, lint, and other particles and micro-organisms that tend to float in the room
- Its design should include such barriers as sealed walls, automatic doors, air-locked doors, ports of various types, or plastic curtains to minimize ingress of contaminants from adjacent support areas or rooms[i.e., glass preparation, equipment wash, compounding & various storage areas].

Clean Room Classifications				
European	United States	International Society of	Maximum № of particles	Maximum № of particles
Grade	Class	Pharm. Eng. Description	per $m^3 \geq$ 0.5μm	per $m^3 \geq$ 5μm
A	100	Critical	3,500	0
B	100	Clean	3,500	0
C	10,000	Controlled	350,000	2,000
D	100,000	Pharmaceutical	3,500,000	20,000

Note:

1. Clean rooms are supplied with positive air pressure, encouraging outward air flow
2. Grade A or Class 100 room is equipped with laminar airflow, originating through a HEPA filter
3. Clean rooms should have daily & weekly cleaning schedules Must be cleaned using at least two types of surface disinfectant per week

Personnel

- They must be neat, orderly and reliable
- They should be in good health and free from dermatological conditions that might increase the microbial load
- If they show symptoms of a head cold, allergies, or similar illness, they should not be permitted in the aseptic area, until recovery is complete

Production Processes

- The processes required for preparing sterile products constitute a series of events initiated with purchase of approved raw materials (drugs, excipients, vehicles, etc.) and primary packaging components (containers, closures, etc.) and ending with the sterile product sealed in its dispensing package
- Each step in the process must be controlled very carefully, so the product has its required quality
- Containers & equipments coming in contact with parenteral preparations must be cleaned meticulously & should be dedicated to a product

Quality control and quality assurance

Sterility test: Confirms that product is free from M.O

Pyrogen test: Evaluates presence of pyrogens in parenteral preparations by a qualitative fever response test in rabbits, precipitation in BET or LAL test

Bacterial Endotoxins Test [BET] **or**

Limulus Amebocyte Lysate (LAL) test

- It is a biochemical test performed in-vitro
- Detects only endotoxin pyrogens of gram-negative bacteria i.e., the most prominent microbial contaminants of sterile products
- Simpler, more rapid & of greater sensitivity than rabbit test
- Following rabbit test, if temp. raise in each 3 rabbits is 0.6 ^{0}C or the sum of 3 rabbits raise in temp. never exceeds 1.4 ^{0}C, then the test product passes rabbit pyrogen test

Ophthalmic and other preparations

- All preparations intended to be applied to the eye, wounded skin, burnt skin or damaged skin and mucus membrane must be sterile and free from grittiness

Unit 10. Current good manufacturing practices [cGMP])

11.1. Building and facilities

11.2. Organization and personnel

11.3. Material, packaging, labeling control

11.4. Production & process controls

11.5. Handling & distribution

What is GMP ?

It is a principle that ensures drug products are safe, pure and effective. How ? By applying validated & consistent production processes

Why GMP is important ?

- Government requirement
- Ensure quality product
- Reduce reprocessing, rejects, recalls
- Satisfied customers needs
- Maintain manufacturing consistency
- Improves company image and reputation

11.1. Building and facilities

- Provides adequate & defined areas for specific unit operations
- Permits effective cleaning
- Prevents contamination or mix-ups
- Ensures orderly conditions
- Ascertains good state of repair

11.2. Organization and personnel

- Have appropriate education, training and experience
- Recruit sufficient number of people
- Receive GMP training
  - Initial & continuing training as relevant to job responsibilities
- Hygiene

– Regular health & eye examinations
– Report adverse health conditions
– Cleanliness requirements
  - No direct skin contact with product, wash hands
  - No jewelry or makeup
– No smoking, eating, drinking, chewing, in operation area

Sanitation

- In place sanitation program to prevent contamination
  1. Limit ***sources*** and ***types*** of contaminations via:
     - Cleaning procedures for facilities & equipment
     - Pest control
     - Environmental monitoring
  2. Documented evidence for each sanitation acts

11.3. Material, packaging, labeling control

A. Raw Materials testing

- Each lot or batch of raw material must be tested for three objectives
  1. Confirm identity of raw materials
  2. provide assurance that quality of drug in dosage form will not be altered by raw material defects
  3. assure that raw materials have the characteristics that provide the desired quantity or yield in the manufacturing process

How?

- Samples of incoming materials are collected and tested before use
- Approved test methods and specifications are used
- Results must conform to specifications for release for use or sale

11.4. Production & process controls

- Written procedures are established and followed
  - Master formula, batch manufacturing order & packaging order
- Critical processes are validated
- 2nd person verification of activities
- Quarantine system
- Lebelling requirements[product, equipment]
- Recall Programme
- Self-Inspection Programme
- Ensure compliance with customers

❖ Validation

The documented act of demonstrating that any procedure, process, equipment, material, activity, or system will consistently lead to the expected results

❖ Qualification

- The act of proving and documenting that equipment or ancillary systems are properly installed, work correctly and comply with specified requirements
- The process used to demonstrate the ability to fulfill specified requirements
- Qualification is part of validation, but individual qualification steps alone do not constitute process validation

Difference between Qualification and Validation?

- To perform a manufacturing process we need personnel, equipment, systems or software along with their respective specifications. These need to be qualified and then, we need to validate the process.
- Therefore, Qualification is directly related to equipment, systems or software and Validation is directly related to the process.

Types of qualifications

- Design Qualification (DQ)
- Installation qualification (IQ): establishes and documents that the unit or system was installed correctly per the manufacturer's specification
- Operational qualification (OQ): establishes and documents that the unit or system operates as intended
- Production qualification (PQ): establishes and documents that the unit or system can fulfil its intended purpose on a reproducible basis when challenged with realistic worst-case conditions

Types of Validation

- Prospective validation (or premarket validation)
- Retrospective validation

- Revalidation

Quality Control Responsibilities

- Testing of bulk components prior to use by production
- Testing of finished product prior to release for sale
- Stability program (in association with QA)

Quality Assurance Responsibilities

- Ensure GMP compliance
- Review batch records, labels
- Release product, based on QC test results
- Authorize all master documents and SOPs
- Training, auditing
- Customer complaints
- Recall

Records

- Record all GMP activities timely as soon as they occur
- Document all GMP activities
- Records must be readily available
- Needed to prove activities were done
- Use Good Documentation Practices (GDP)

Good Documentation Practices

- Documentation must be:
  - ❖permanent (black or blue ink)
  - ❖legible, clear, concise
  - ❖accurate
  - ❖timely
  - ❖consistent
  - ❖complete

Samples and Stability

- **Samples**
  - Retain samples of each lot of raw material and finished product for specified period of time
- **Stability**
  - Establish the length of time in which the product meets all specifications
  - Monitor the drug for this period of time

11.6. Handling & distribution

- Warehousing and distribution
- There should be SOP for:
  - quarantine of drug products before release QC unit
  - storage of drug products under appropriate storage conditions
  - ensuring use of the oldest approved stock first
  - documenting distribution of drug product

END Of THE COURSE

Write true or false & give reasons for each answer [10/07/2014 E.C]

1. Formulation optimization refers to increasing quantities of each components of the formulation
2. Parentral & oral grade inputs differ in their chemical properties
3. Ageing of shellac is accompanied by prolonging tablet disintegration time
4. Gelatin gel pass gel strength test if a plunger penetrate via the gel kept at 10 ^{o}C
5. Gelatin shell filled with aldehyde based medicated powder passes disintegration test
6. Compounding of parentral products occurs in grade-A room
7. Press & enteric coated tablets release their drug content in the small intestine

Write true or false & give reasons for each answer [11/07/2014 E.C]

1. Parentral & oral grade powder inputs differ in their particle sizes
2. Formulation optimization necessarily refers to enhancing amount of each components of the formulation
3. Repolymerization of shellac is accompanied by prolonging coated tablet disintegration time
4. Gelatin shell filled with aldehyde containing medicated powder passes disintegration test
5. Filling of parentral products is conducted in grade-B room
6. Enteric coated & Press tablets release their drug content only in the small intestine
7. Gelatin gel pass gel strength test if a plunger penetrates deep about 4mm via the gel kept at 10 ^{o}C